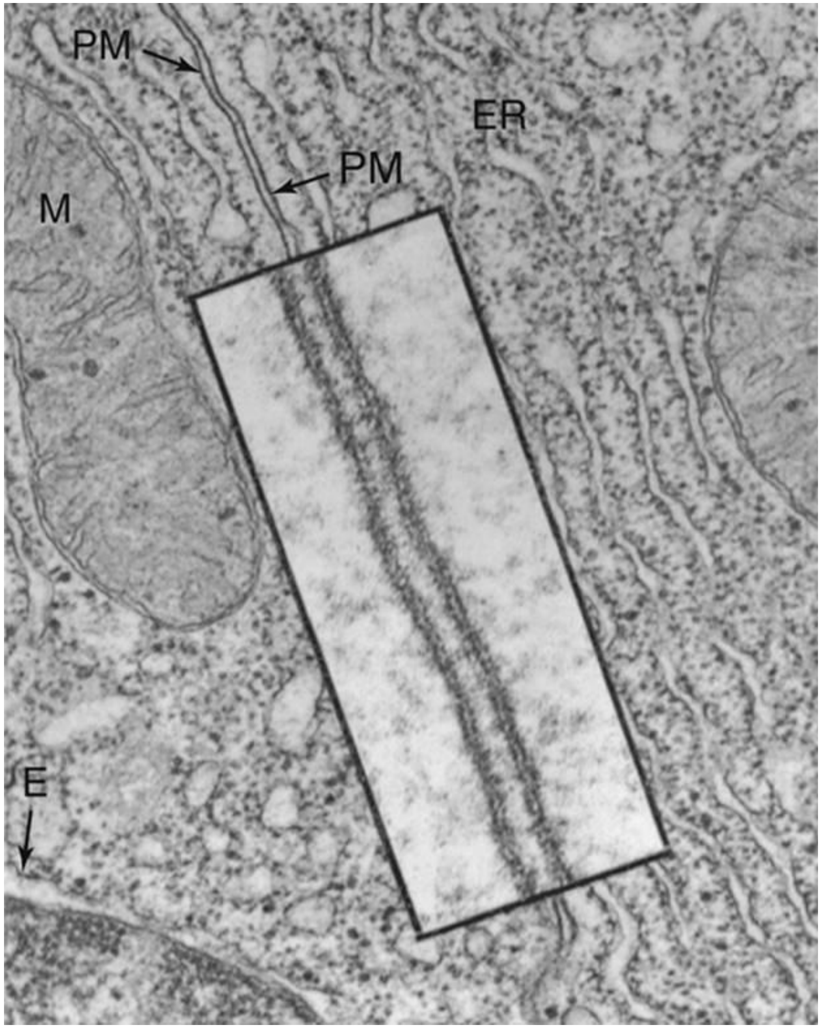
# Structure of biological membranes

# Transport through membranes

Lippincott Illustrated Reviews. Cell and Molecular Biology Third Edition. Nalini Chandar, Susan Viselli

chapters 3, 13, 14, 15, 16

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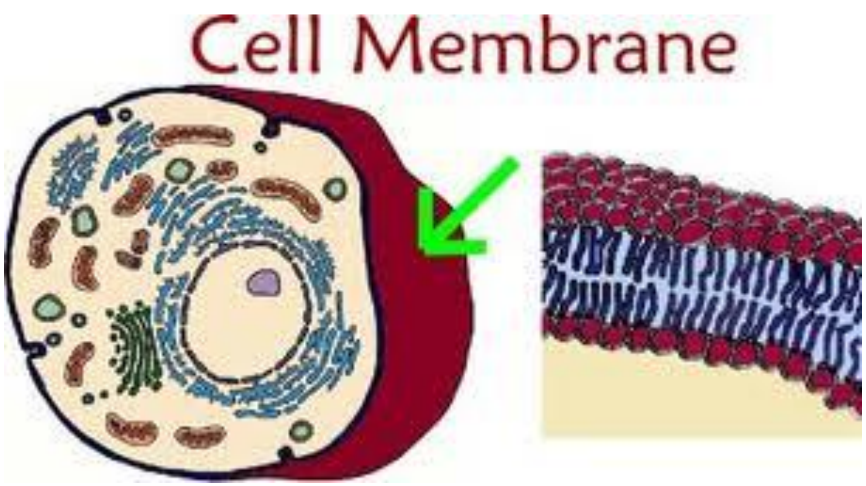
Biological membranes
in eukaryotic cells

Błona komórkowa

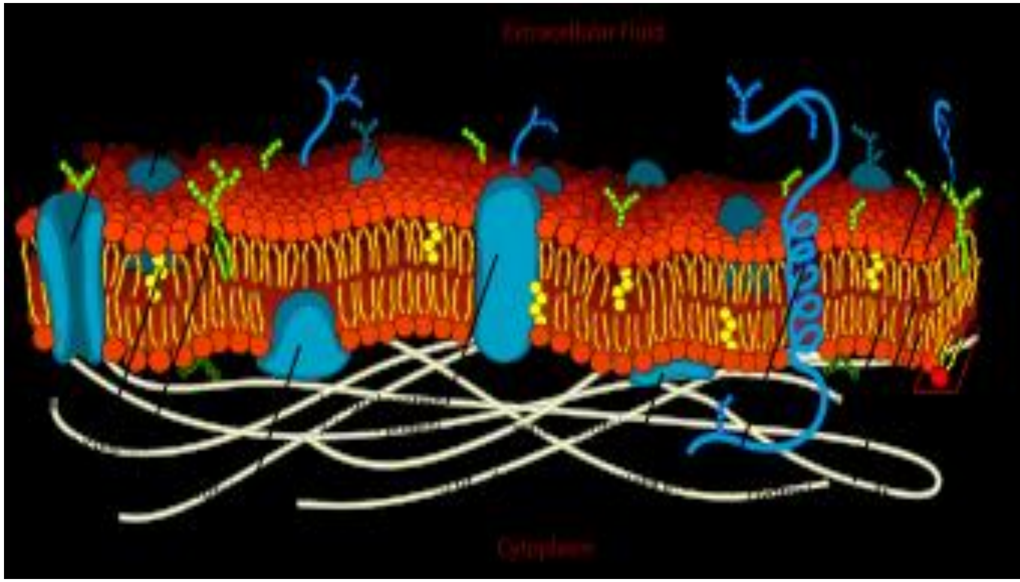



Intracellular membranes

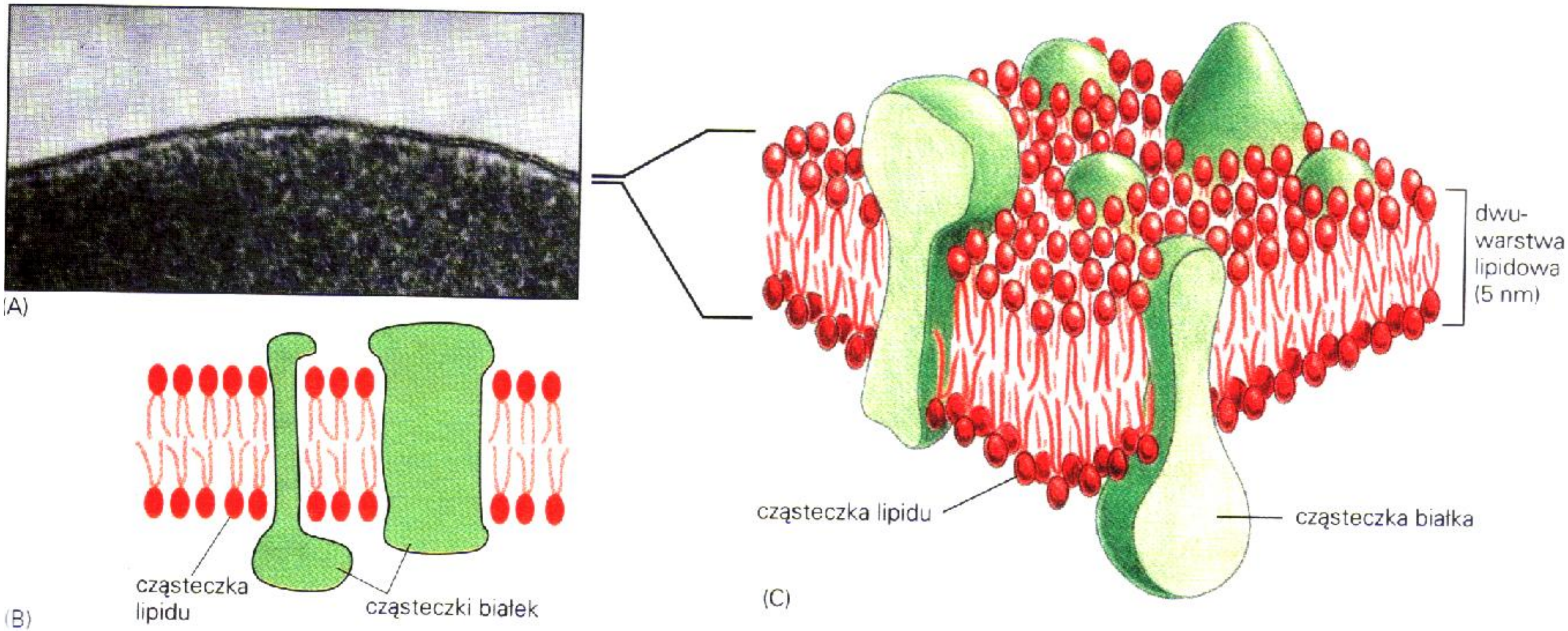
Endoplasmic reticulum
Golgi apparatus
Lysosomes
Peroxisomes
Endosomes
Transport bubbles
Nuclear envelope
Mitochondrial membranes

**Biological membrane** - biomembrane, a protein-lipid complex the basic structure of cell structure

- Separation of the cell from the environment
- Transport of molecules to and from the cell
- Cell-cell, cell-matrix interactions
- Ion and other molecules concentrations
- Signal transmission
- Signal transduction
- Formation of intracellular compartments
- Intracellular transport
- Energy generation and
- storage

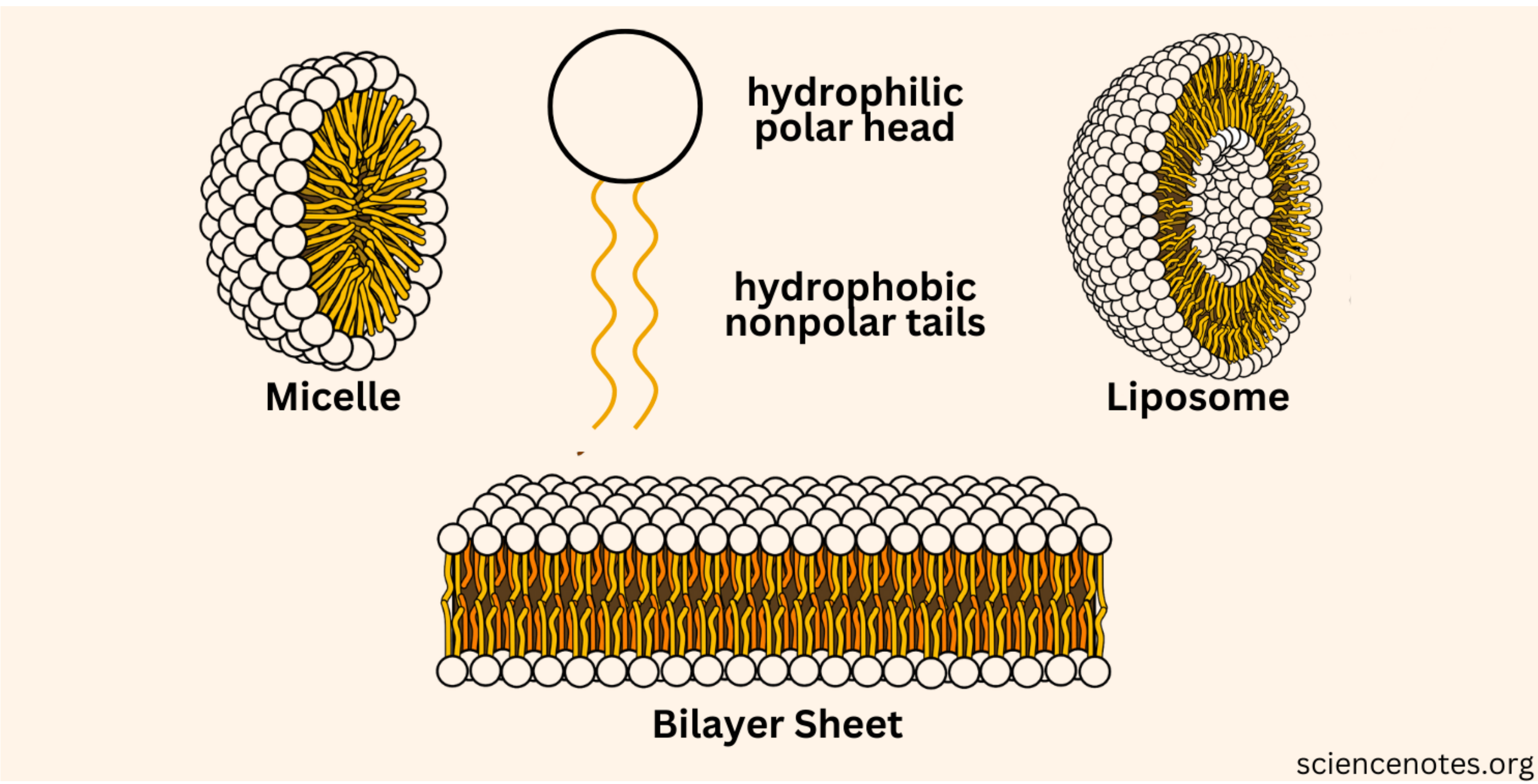


# Diagram of the general structure of the biological membrane
# Liquid mosaic model



# FLUIDITY, ASYMMETRY, SEMI-PERMEABILITY

The characteristic structure of the membrane is made by the amphipathy of the molecules - **lipids** - composed of a non-polar hydrocarbon tails and a polar head, thanks to which the lipids are arranged in a **bilayer** or spherical vesicles (liposomes, micelles).



# Cell membrane lipids

Phospholipids

Glycerol or sphingosine esters

Phosphatidylcholine (lecithin)
Phosphatidylserine
Phosphatidylethanolamine
Phosphatidylinositol

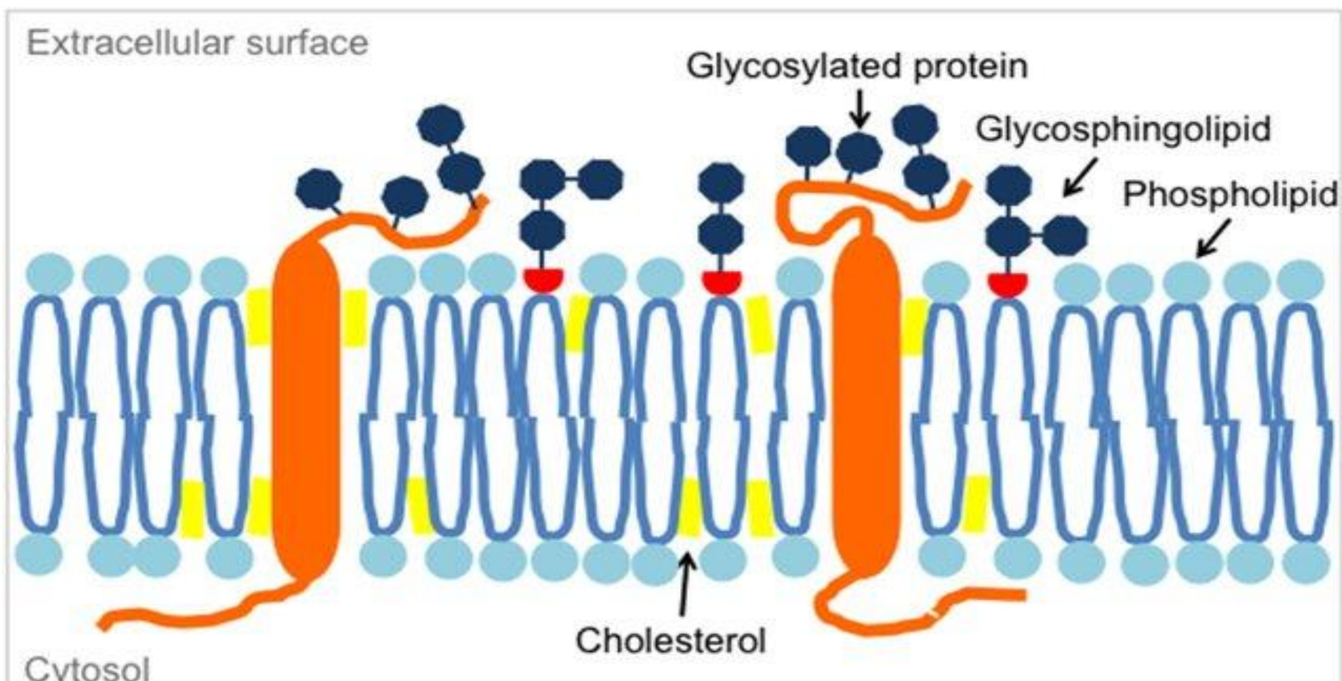
Sphingomyelin

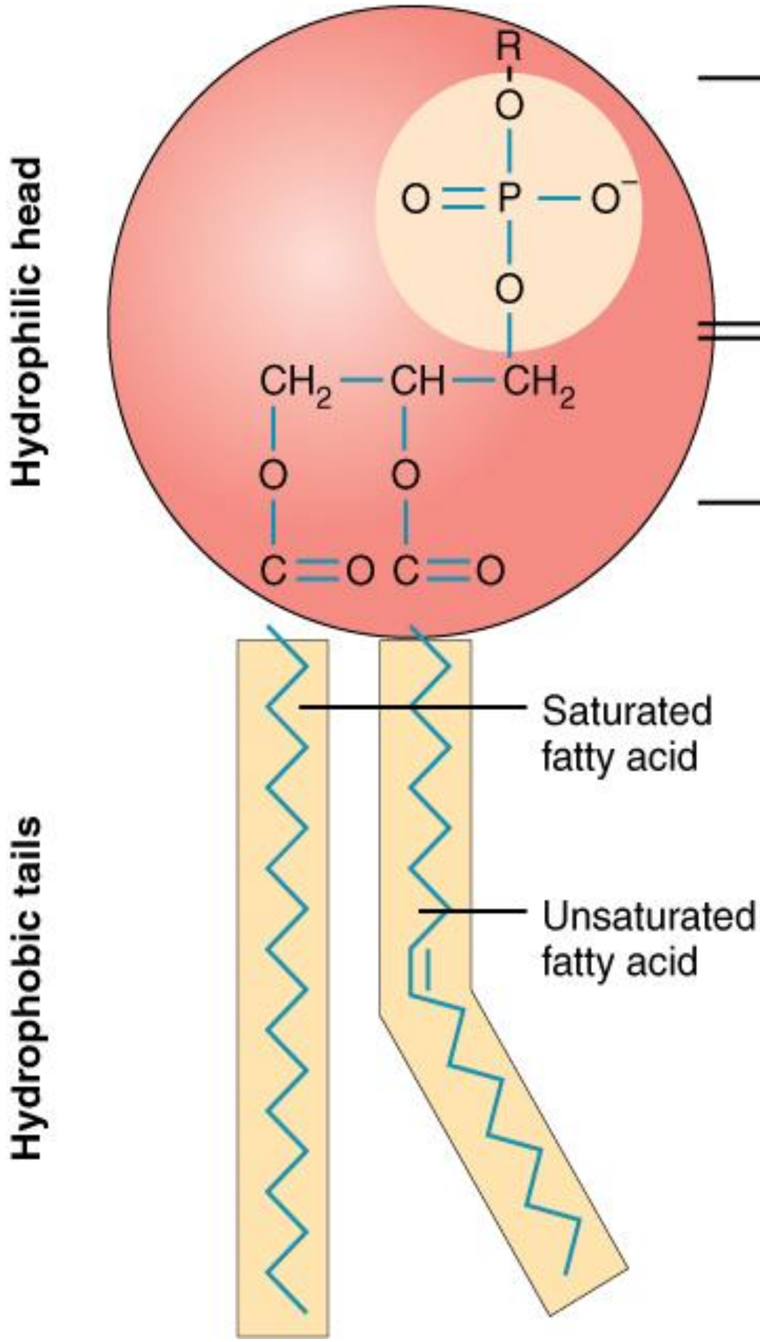
Sterols

Cholesterol

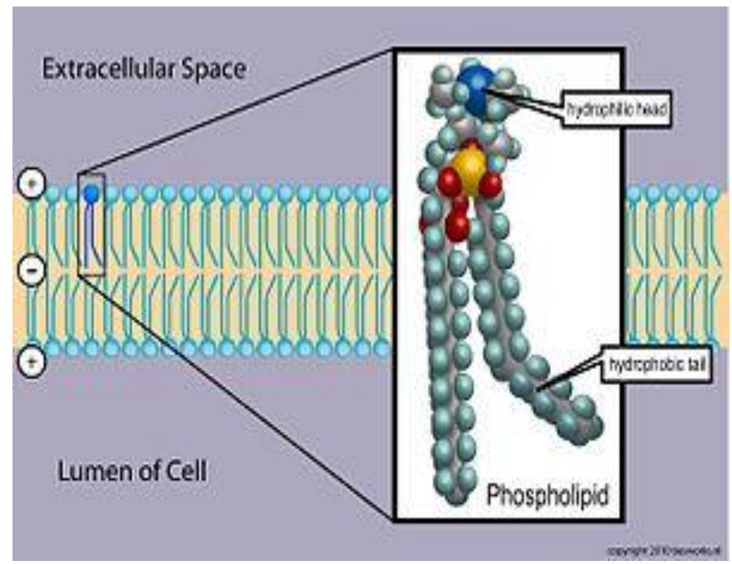
Glycolipids

(glycosphingolipids)

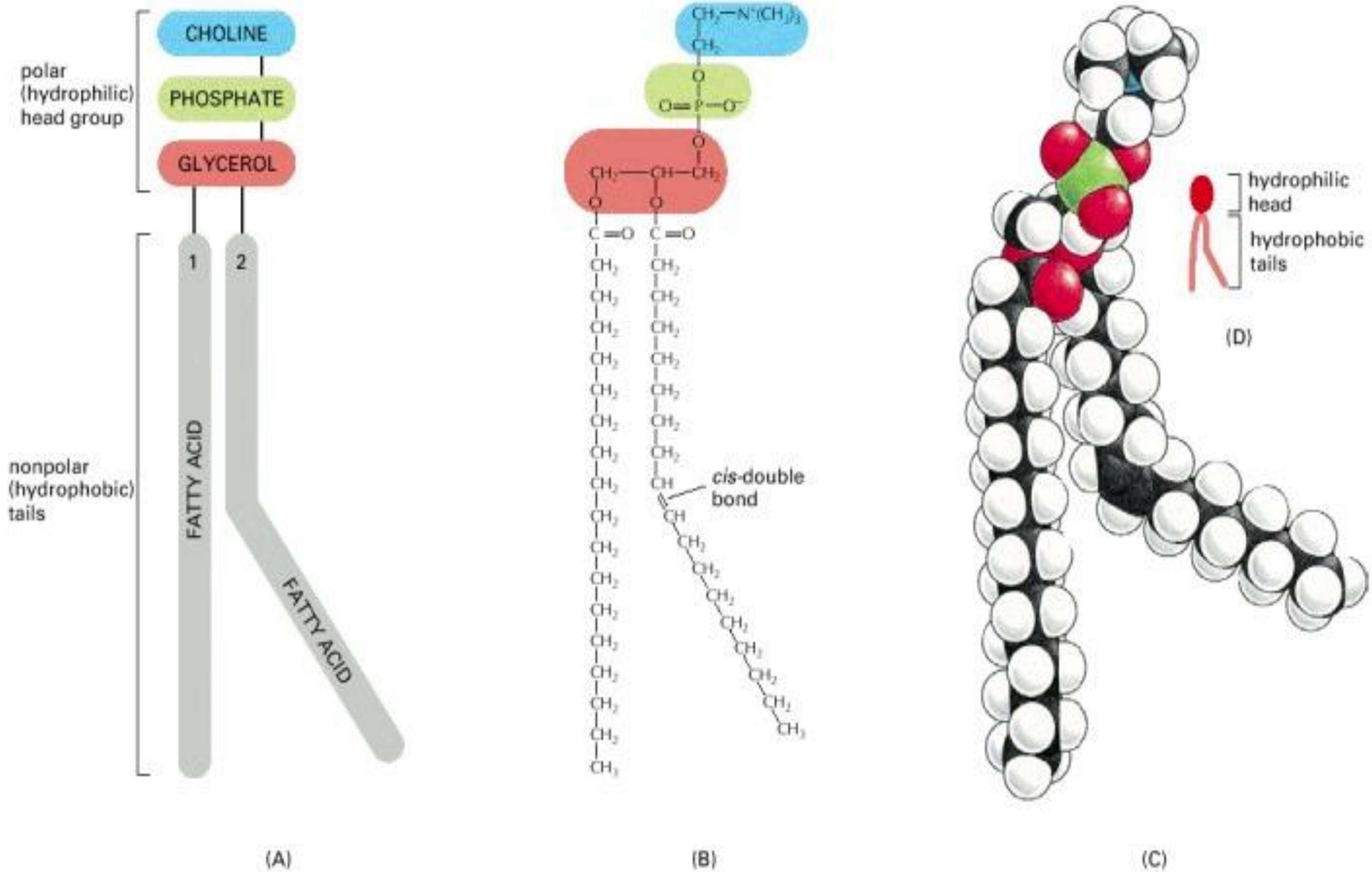





R – choline,
serine,
ethanolamine,
inositol

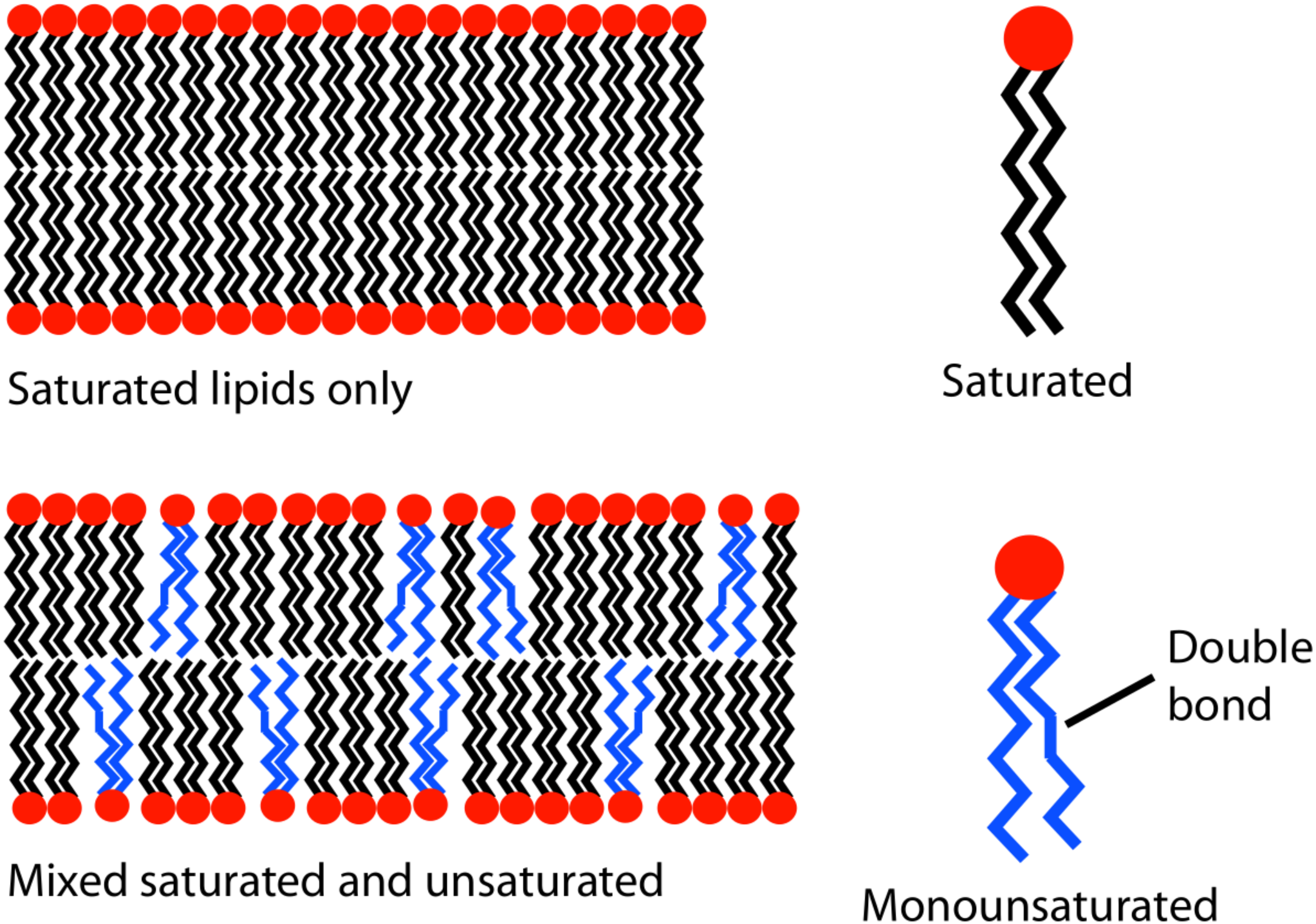



Each phospholipid is composed of hydrophilic head and hydrophobic tail – amphipathic molecule



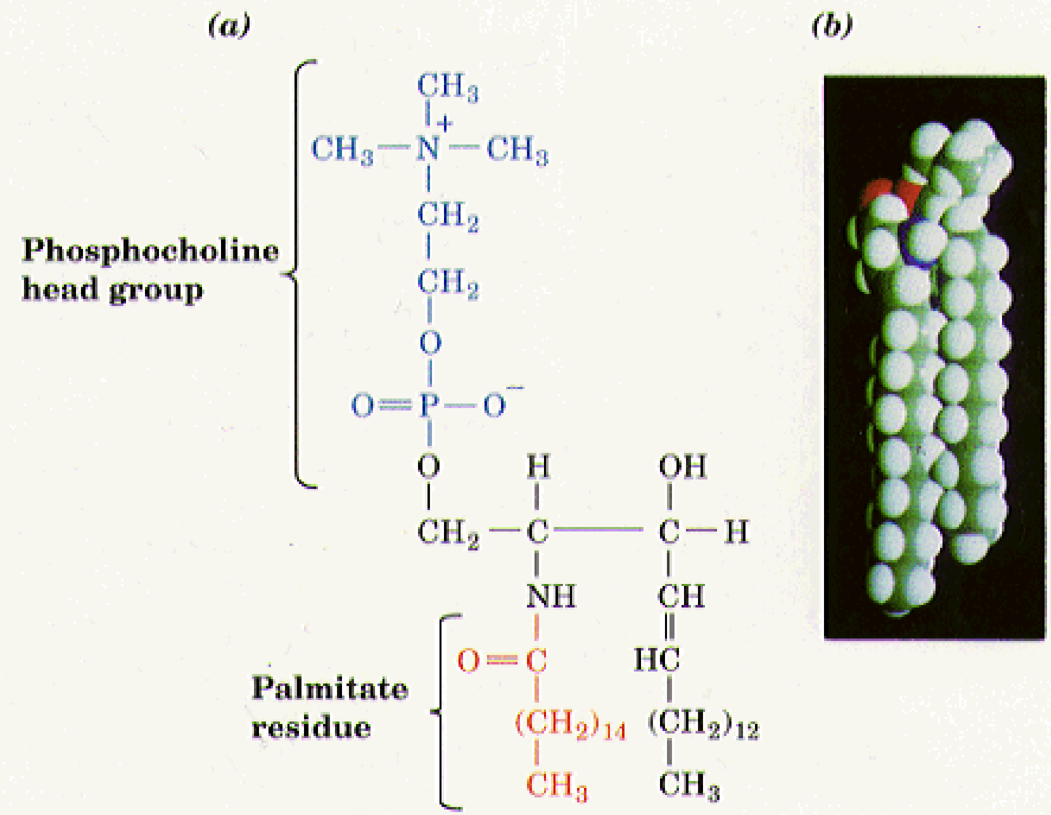
CHOLINE
PHOSPHATE
GLYCEROL
polar
(hydrophilic)
head group
nonpolar
(hydrophobic)
tails
1
2
FATTY ACID
FATTY ACID
cis-double
bond
hydrophilic
head
hydrophobic
tails
(D)
(A)
(B)
(C)

# Płynność błon



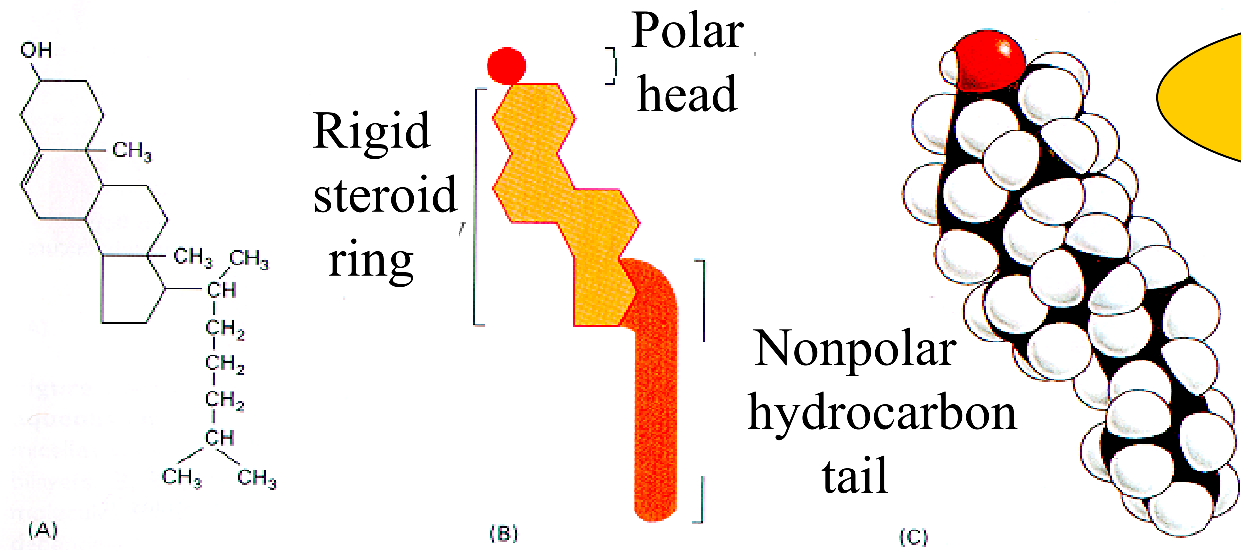
# Sphingomyelin

sphingosine,
fatty acid,
phosphate group,
choline



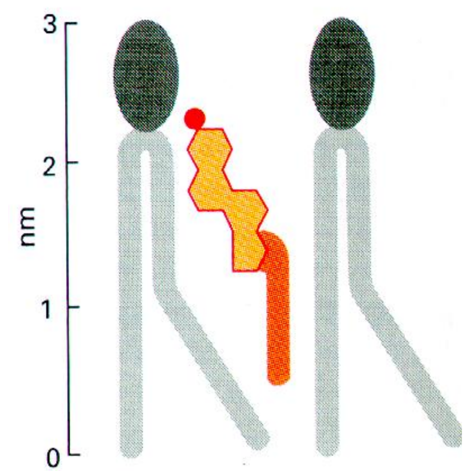

A sphingomyelin

# Cholesterol structure and its effect on membrane fluidity



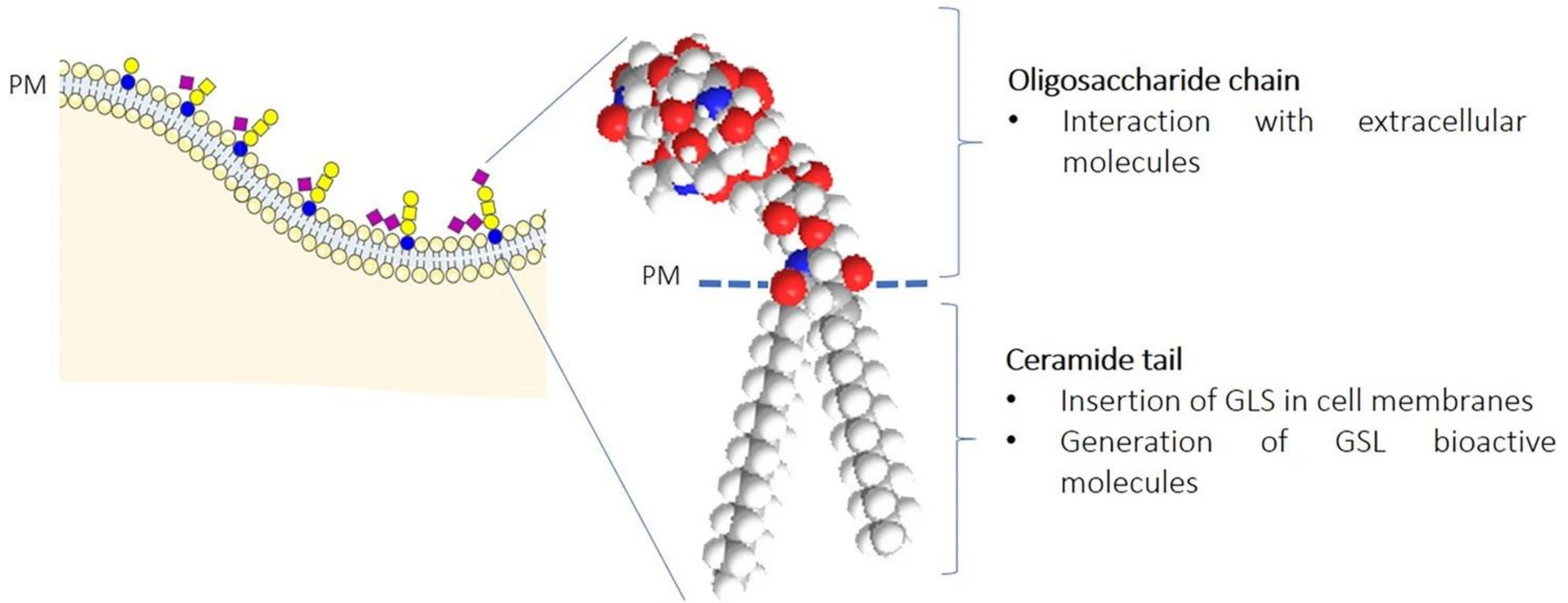

Structure of cholesterol

- an essential structural component of animal cell membranes that is required to establish proper membrane permeability and fluidity.

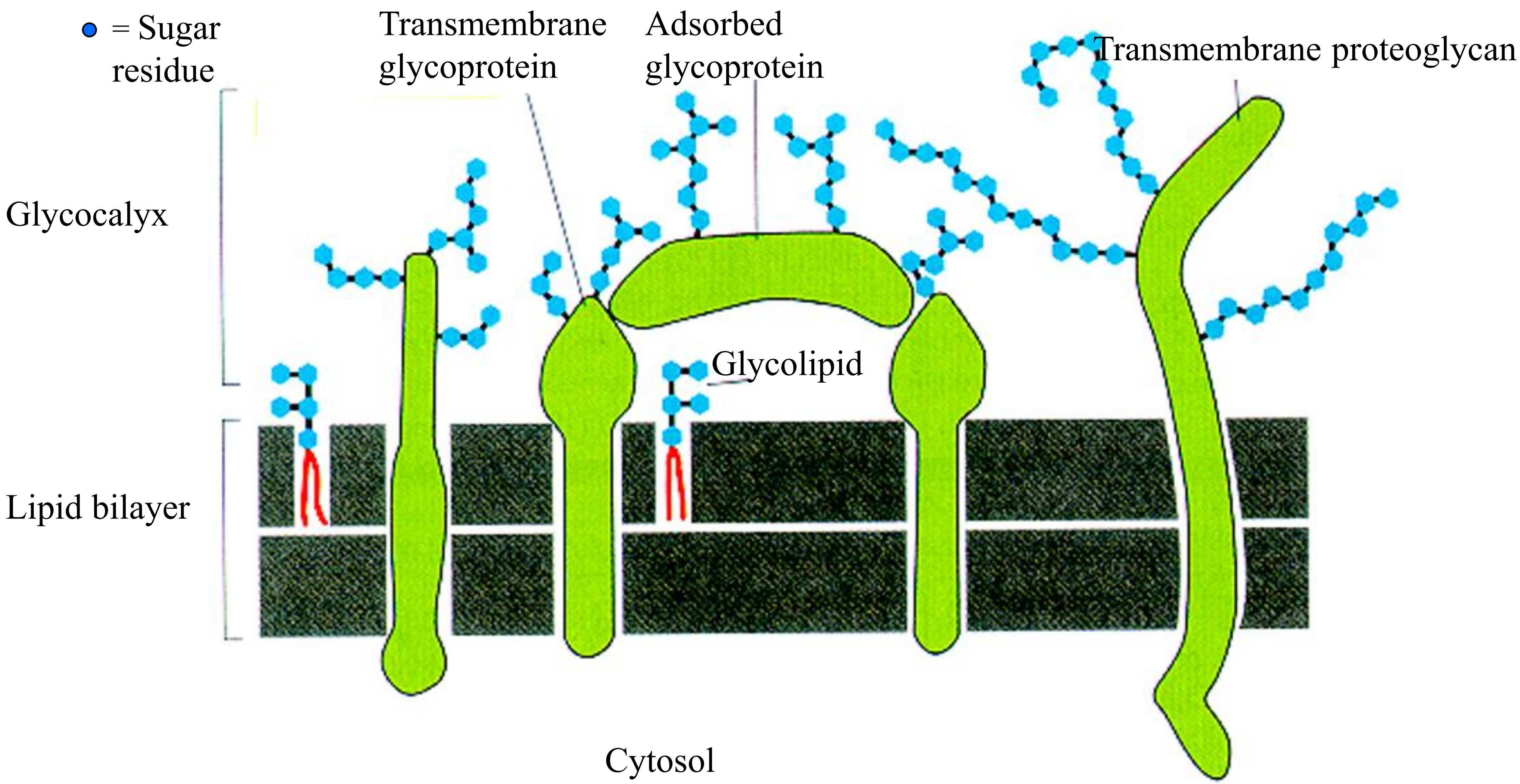


# Glycosphingolipids

- sphingolipids with carbohydrate attached, which are part of the cell membrane. They consist of a hydrophobic ceramide part and a glycosidic-bound carbohydrate part. Oligosaccharides remain outside the cell membrane, where they mediate cell adhesion or cell-cell interactions



# Asymmetry - glycocalyx structure

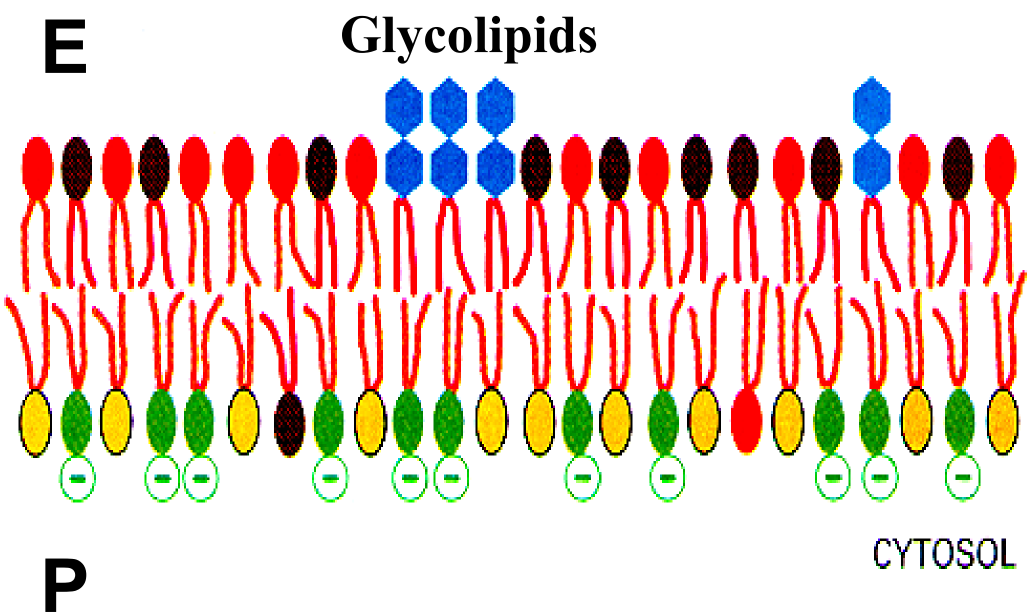



Glycocalyx - pericellular matrix or cell coat - a layer of glycoproteins and glycolipids that surround the cell membrane (glycophospholipids and glycoproteins).

Protects the cell from chemical and physical injury

responsible for recognition and cell-cell, cell-ECM interactions

# Asymmetry - distribution of phospholipids




Sphingomyelin

Phosphatidylcholine

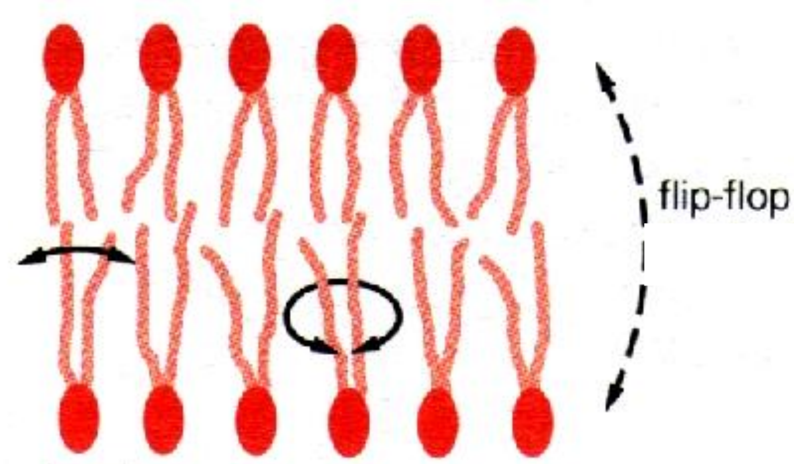
Phosphatidylethanolamine,

Phosphatidylserine,
Phosphatidylinositol

# Cell membrane asymmetry

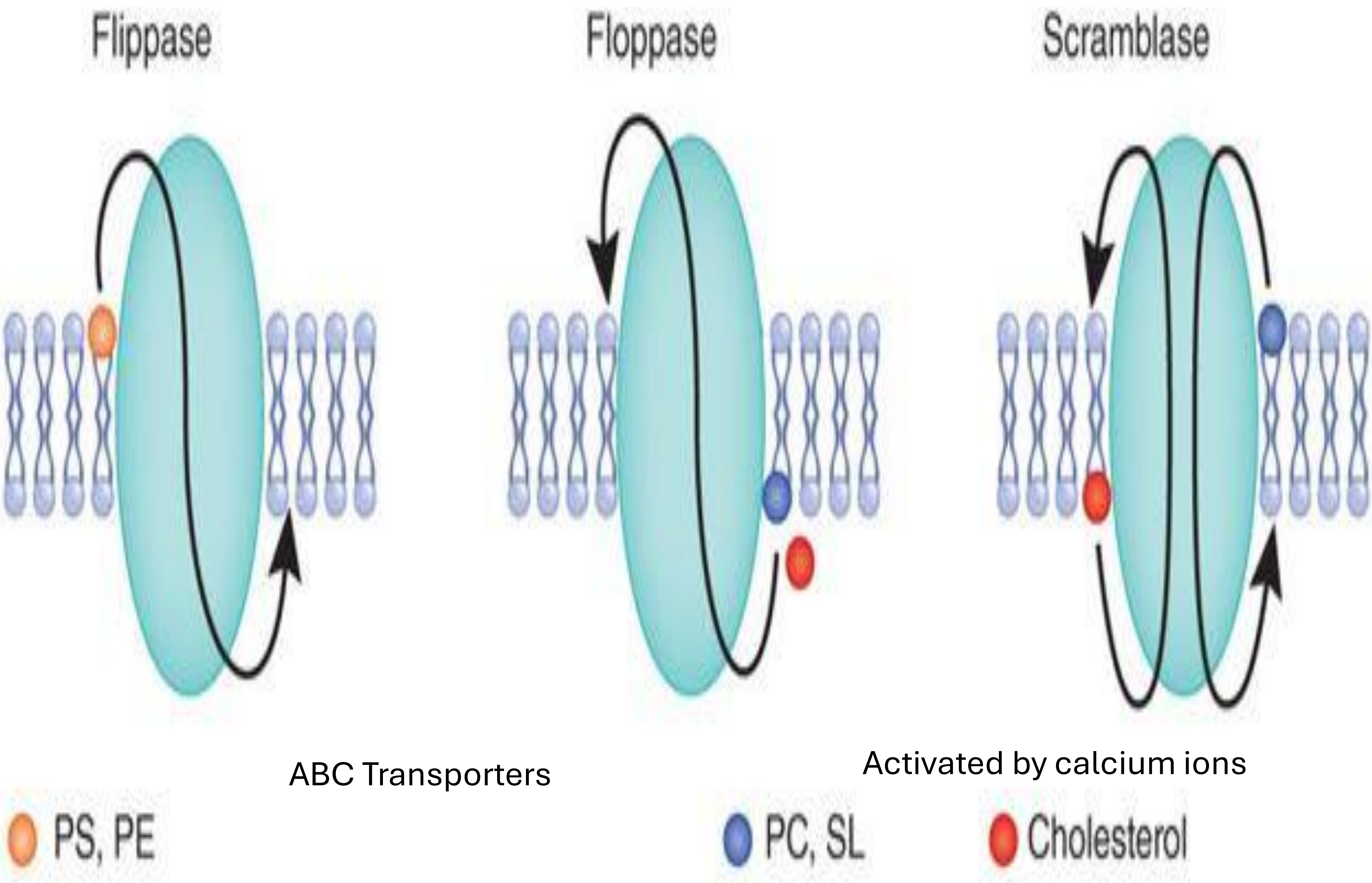
| ***Lipids*** | ***% (total)*** | ***E*** | ***P*** |
|---|---|---|---|
| Cholesterol | **23%** | 50% | 50% |
| Phosphatidylinositol | **1%** | - | 100% |
| Phosphatidylethanolamine | **18%** | 20% | 80% |
| Phosphatidylcholine | **17%** | 80% | 20% |
| Phosphatidylserine | **7%** | - | 100% |
| Sphingomyelin | **18%** | 90% | 10% |
| Glycolipids | **3%** | 100% | - |

# Movements of lipids in membranes



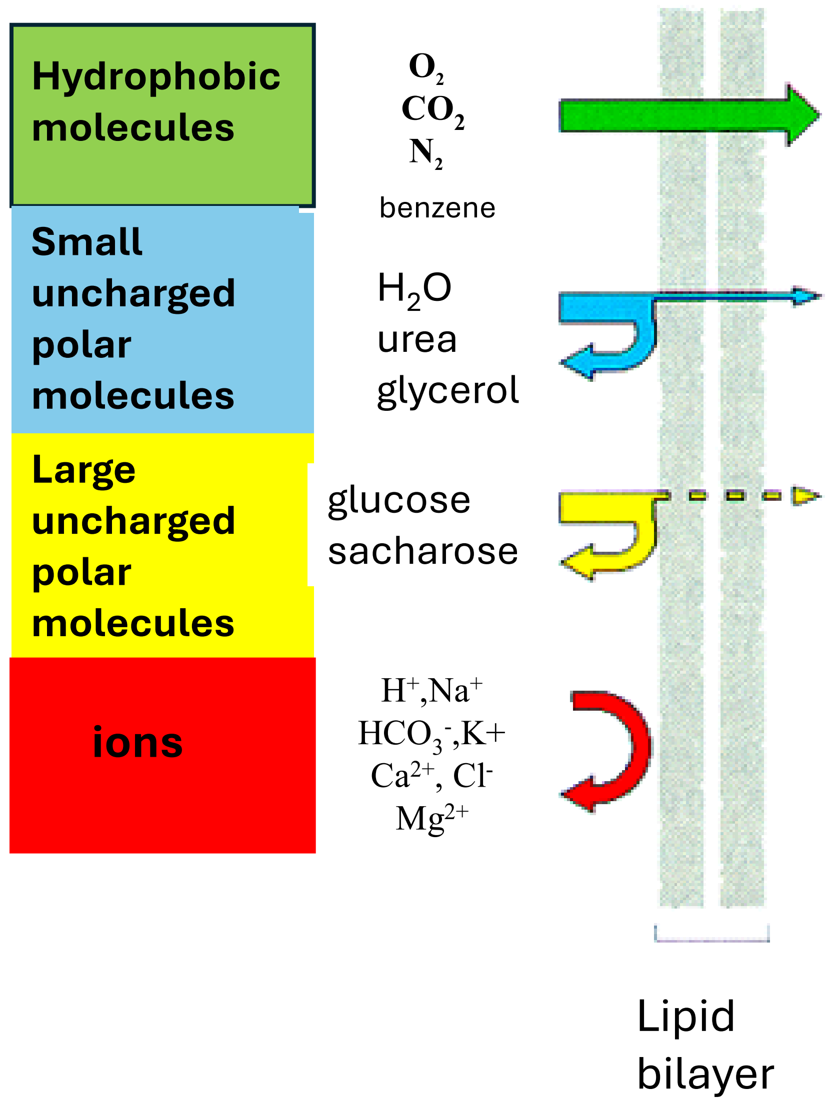

Movements **flip-flop** are catalysed by **enzymes – flippase, floppase, scramblase**

Lateral diffusion is the sideway movement of lipids and proteins within a single leaflet of a biological membrane
Rotational movement
Transverse diffusion (flip-flop)
Intermembrane Transport

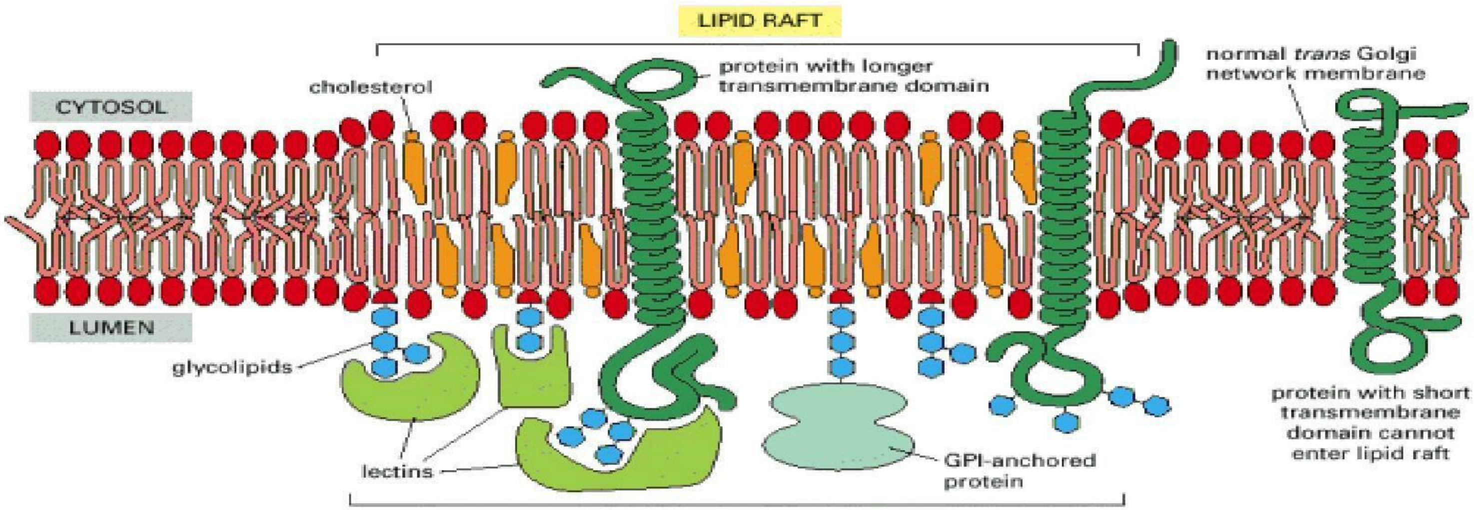


Flippase
Floppase
Scramblase
ABC Transporters
Activated by calcium ions
PS, PE
PC, SL
Cholesterol

# Membrane permeability



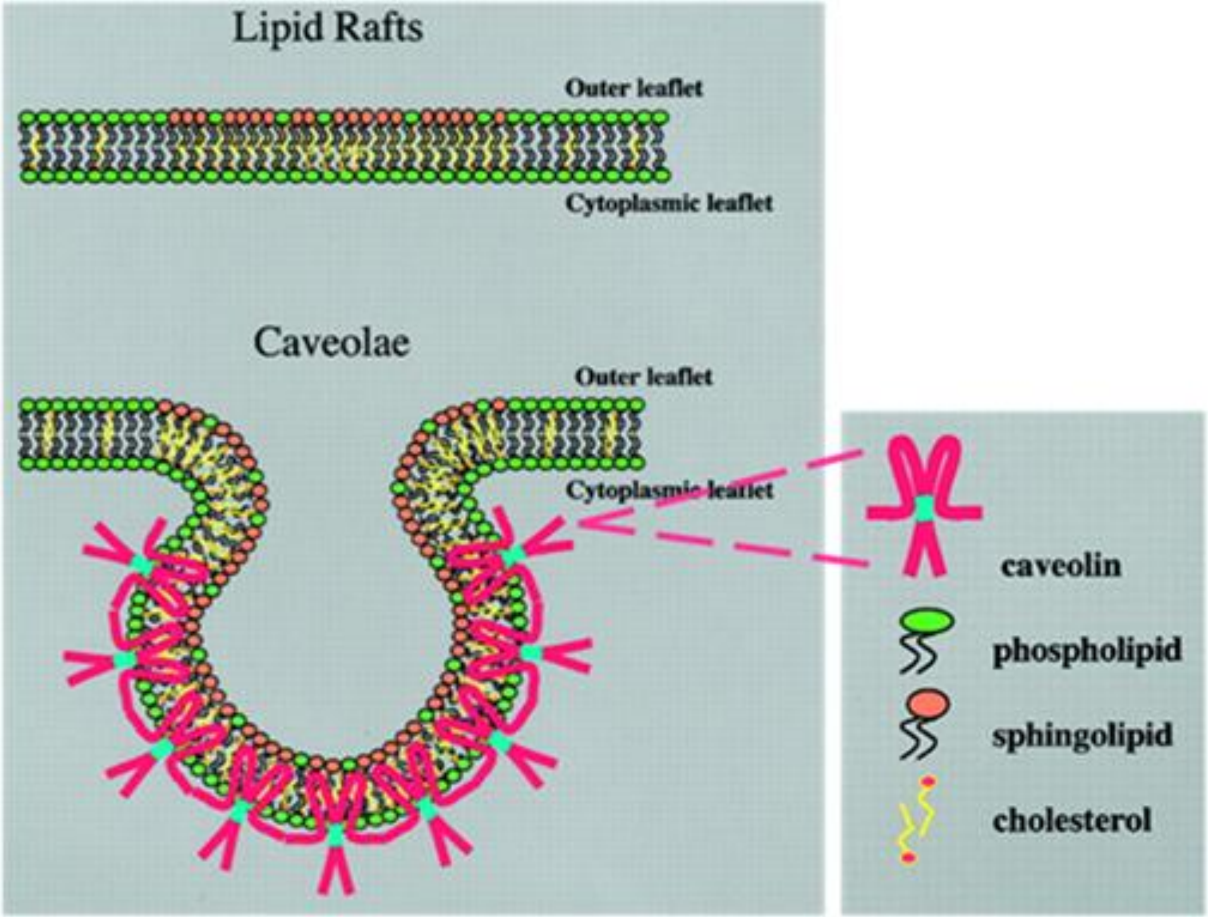
# The cell membrane is not homogeneous
# **Lipid raft - a site with reduced lateral diffusion**



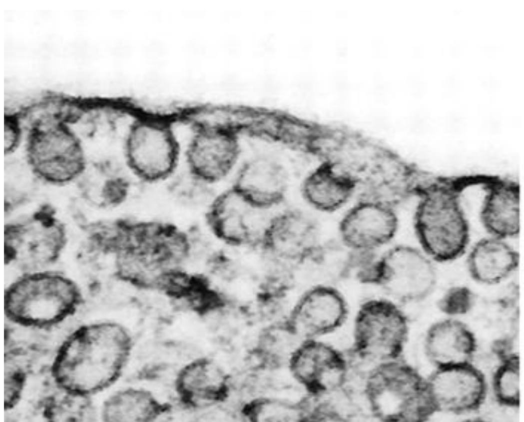

- Lipid rafts are small, specialized sites in the membrane where saturated phospholipids are concentrated – **sphingolipids,cholesterol and proteins**
- Lipid rafts are characterized by reduced fluidity within the raft.
- **Lipid rafts accumulate some proteins, especially receptor proteins and caveolins**. It enables the production of **caveolae -** small cavities in the cell membrane where various receptors accumulate.

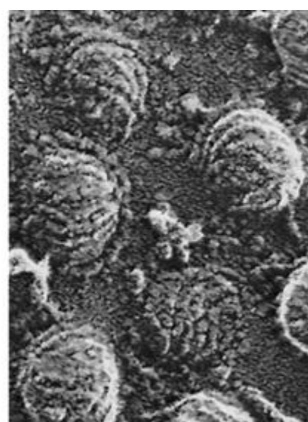
## CAVEOLI

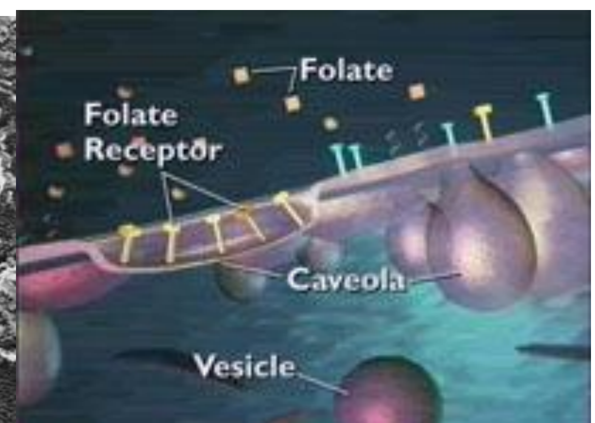
Small (50–100 nanometers) invaginations of the plasma membrane in lipid rafts in many cell types, especially endothelial cells and adipocytes. They are rich in cholesterol and sphingolipids and have the function of signal transduction. They also play a role in endocytosis and the capture of bacteria and viruses.



Caveoli are responsible for caveolin-dependent endocytosis. They can fuse with early endosomes or caveosomes. The caveosome is a cell compartment with a neutral pH.
This type of endocytosis is used for albumin transcytosis in endothelial cells or for the internalization of the insulin receptor in primary adipocytes.
It is also a type of receptor-mediated endocytosis in which folic acid molecules are transported across the plasma membrane of the cell. The molecules that are transported by the caveoli can be deposited in the cytosol.

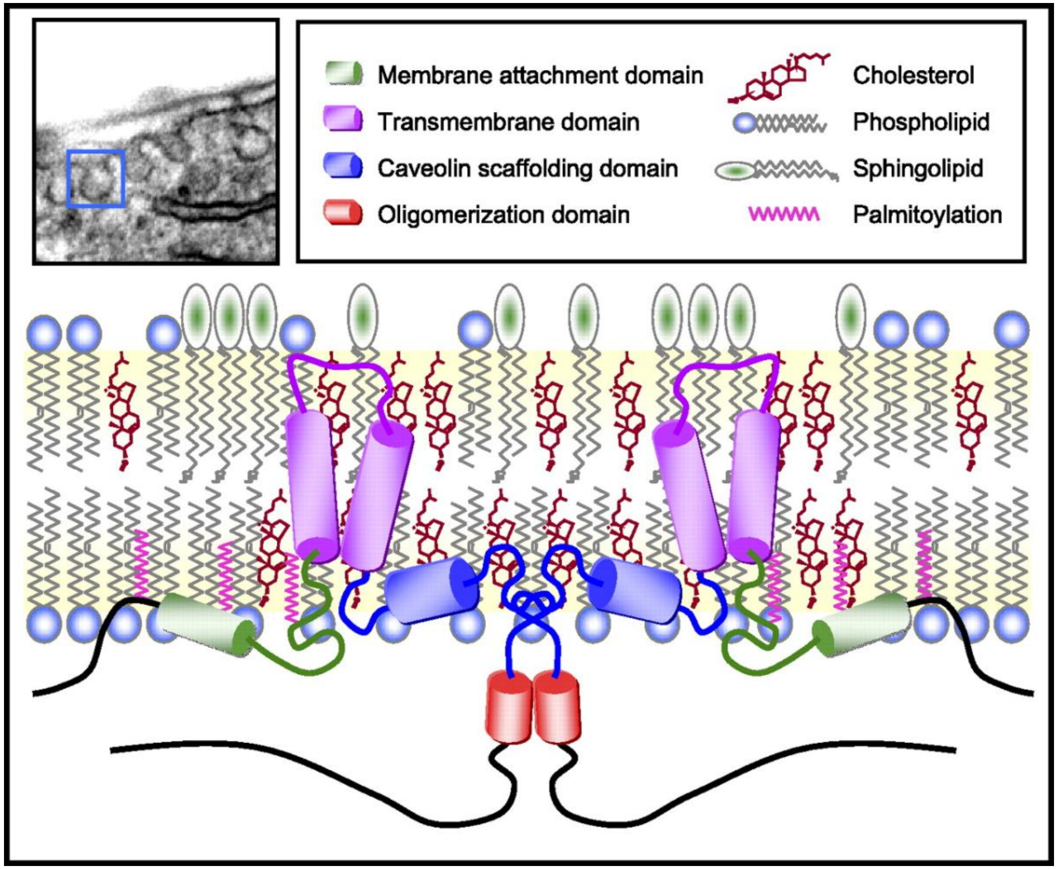






# Caveolins

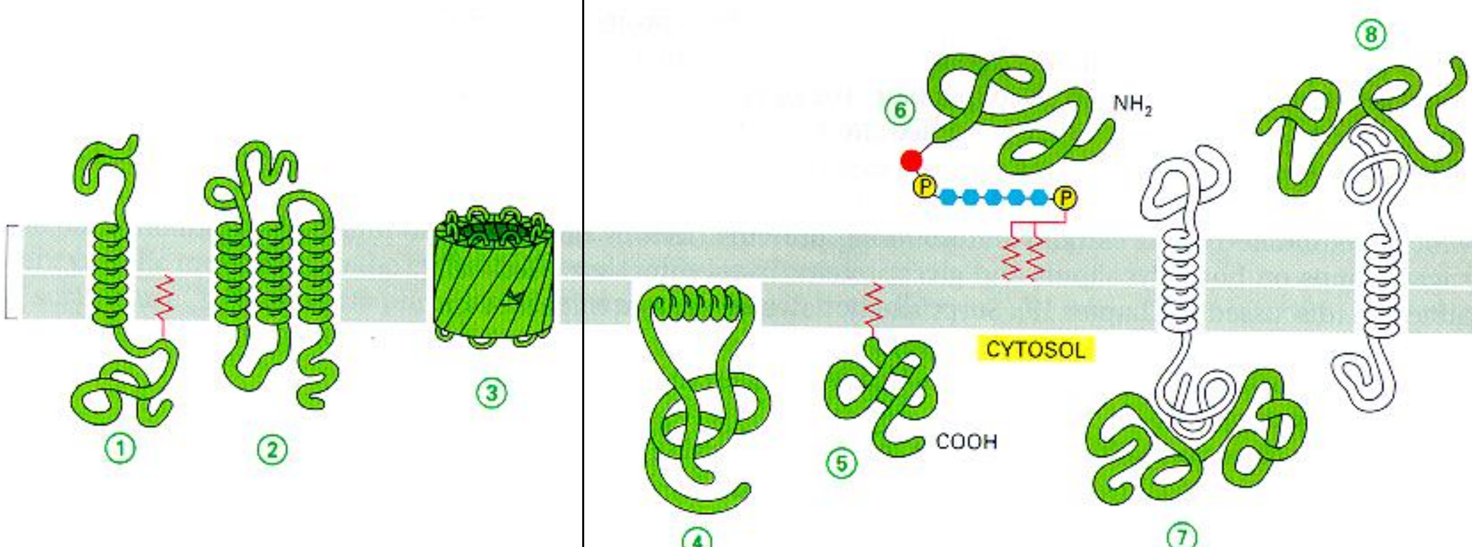
The formation and maintenance of caveolin is determined by caveolin proteins - Cav1, Cav2 and Cav3.
Caveolins combine with lipid rafts and form oligomers (14-16 molecules). These oligomerized proteins form caveoli.



# Cell membrane proteins
## Transporting, anchoring, receptors, enzymes

Transmembrane proteins

Surface proteins



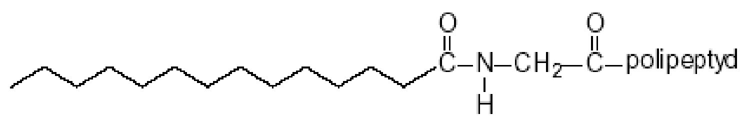

(1) Single alpha helix (additionally sometimes bound fatty acids)
(2) As multiple alpha helixes,
(3) As a collapsed beta sheet.

(4) The hydrophobic part alpha helixes.
(5) Covalently bound fatty chain
**- myristic acid or isoprenyl residues**
(6) Oligosaccharide combining with phosphatidylinositol
(7, 8) Non-covalent interactions with other membrane proteins

# Lipid modifications for protein anchoring

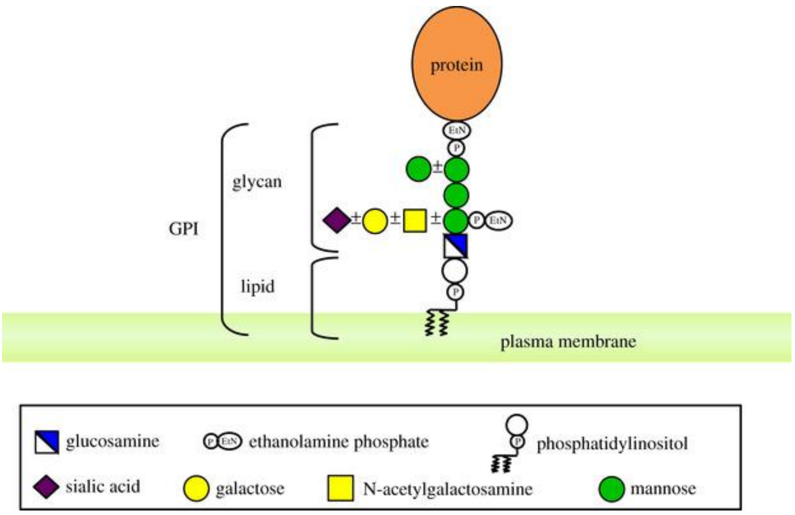
## Proteins anchored by a lipid residue are characterized by high mobility in the membrane

**Myristillation, prenylation, farnesylation**– posttranslational modifications of proteins, consisting in the attachment of several carbon lipid residues, which enables the anchoring of proteins in the cell membrane (P surface)

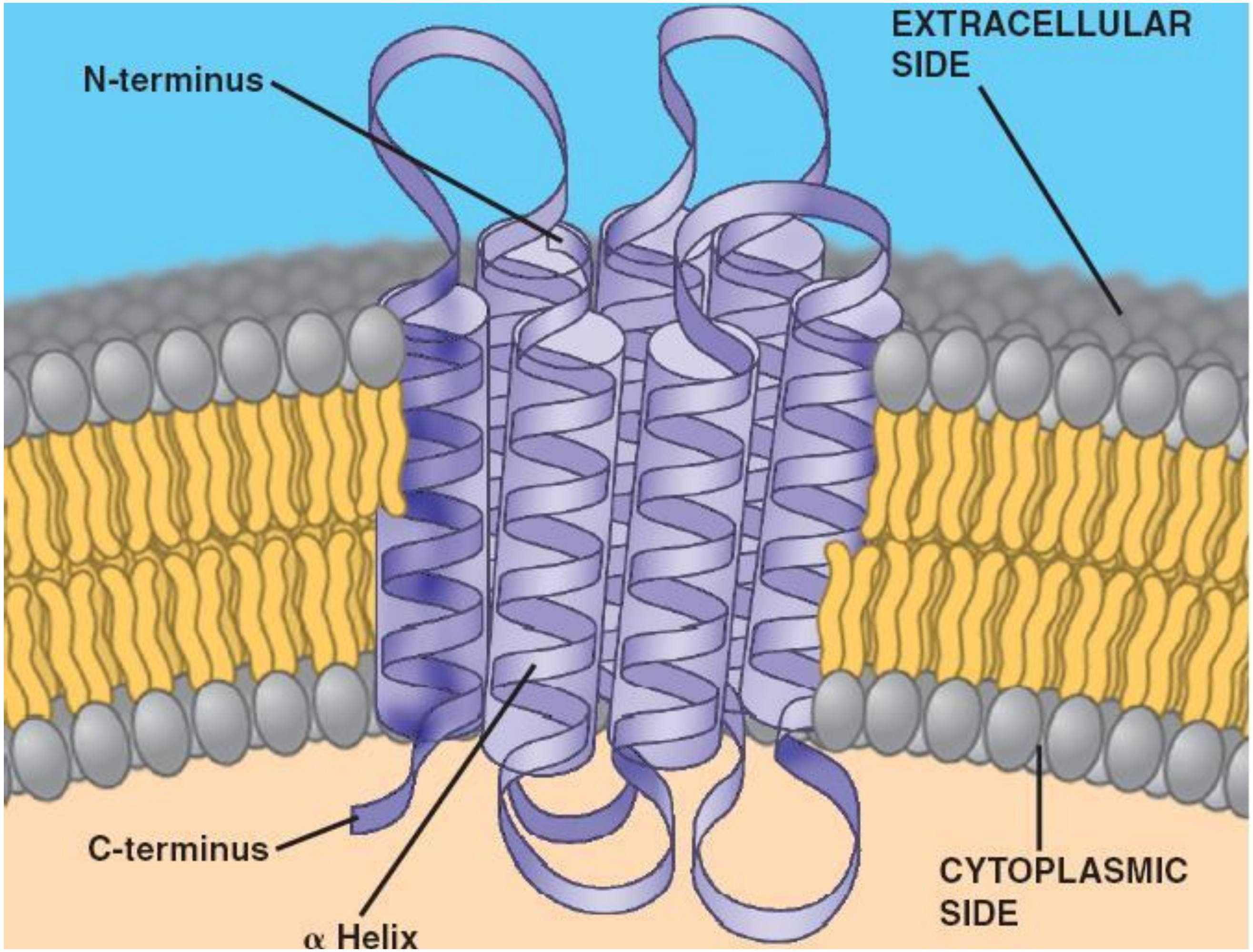



N-mirystoiloglicyna-N-końca polipeptydu

Glycosylphosphatidylinositol, glycophosphatidylinositol, GPI – a glycolipid used in the cell for posttranslationl modification of proteins. Allows proteins to be anchored in the cell membrane (E-side, lipid rafts)

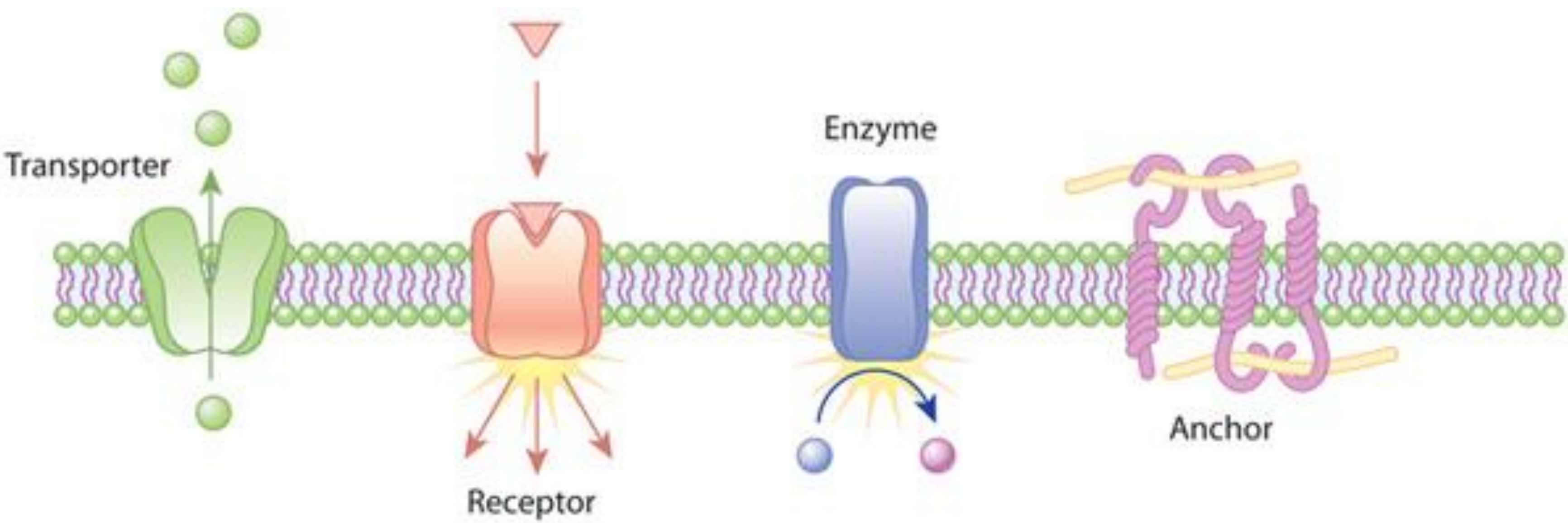


## Multipass protein




- pass through the membrane several times
- have binding sites for signal molecules

## FUNCTIONS OF TRANSMEMBRANE PROTEINS



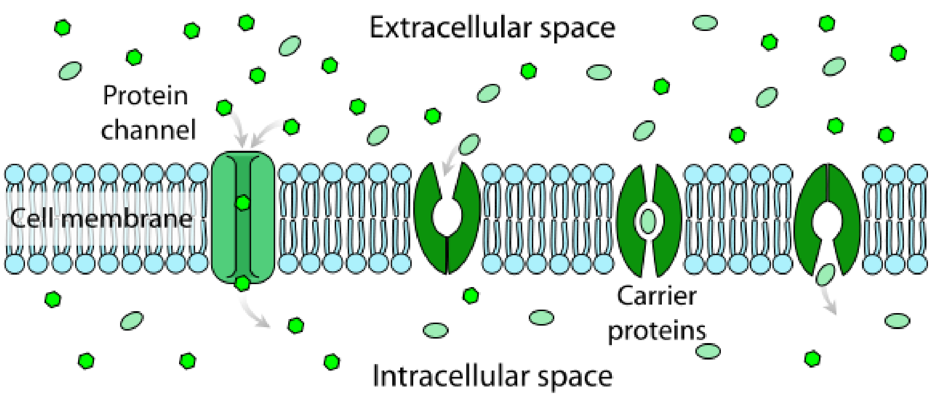

**Transporters** – carry the molecule from one side of the plasma membrane to the other
**Receptors –** bind the extracellular molecule and activate the intracellular process
**Enzymes –** transform the molecule into another form
**Anchor proteins –** combine intracellular structures with extracellular structures

# TRANSPORT PROTEINS

facilitate the transfer of hydrophilic molecules across the cell membranę

- Channel proteins
- Carrier proteins

Transport of ions and small molecules across the plasma membrane



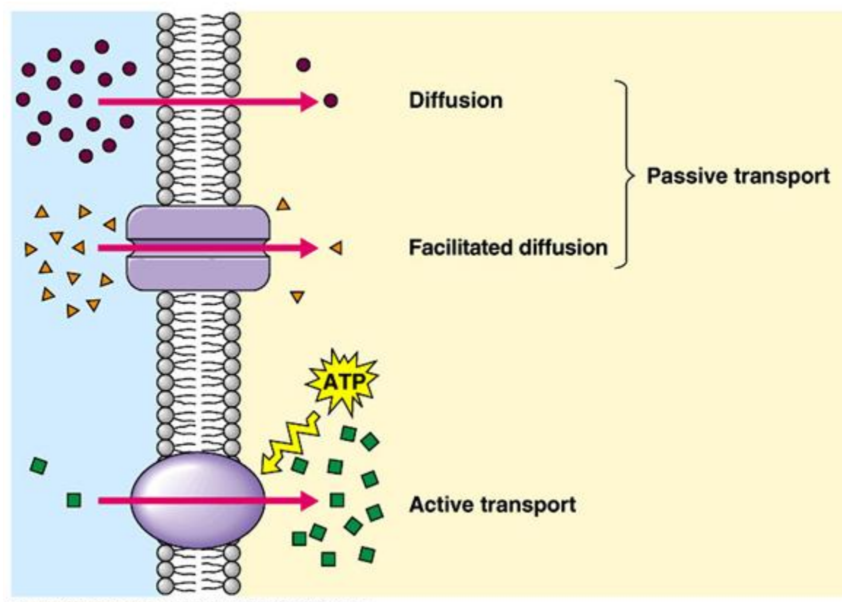

Kinds of transport:

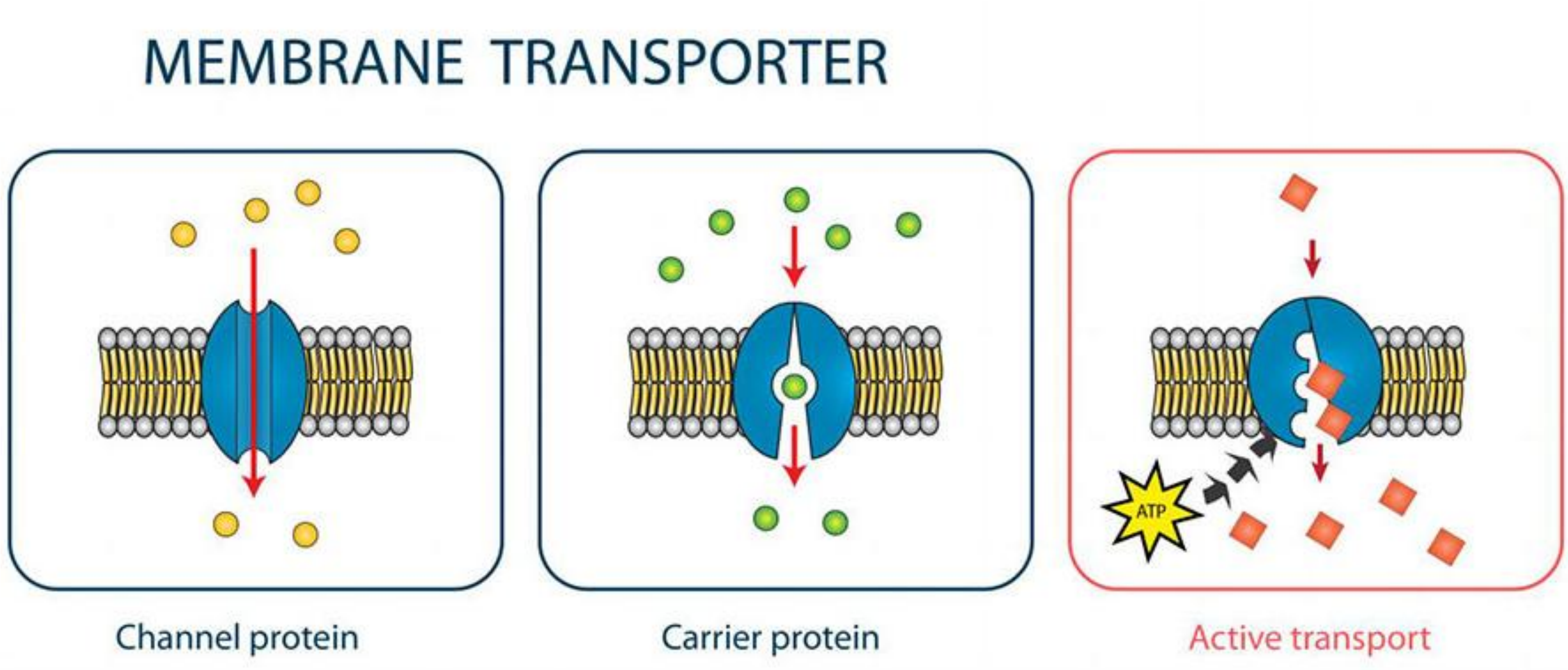
1. **Passive transport–**

Simple diffusion ($O_2$, $CO_2$, $N_2$, $H_2O$, glycerol, ethanol)

Facilitated diffusion (channel and carrier proteins)

2. **Active transport –** energy-requiring transport (carrier proteins only)






CHANNEL PROTEINS

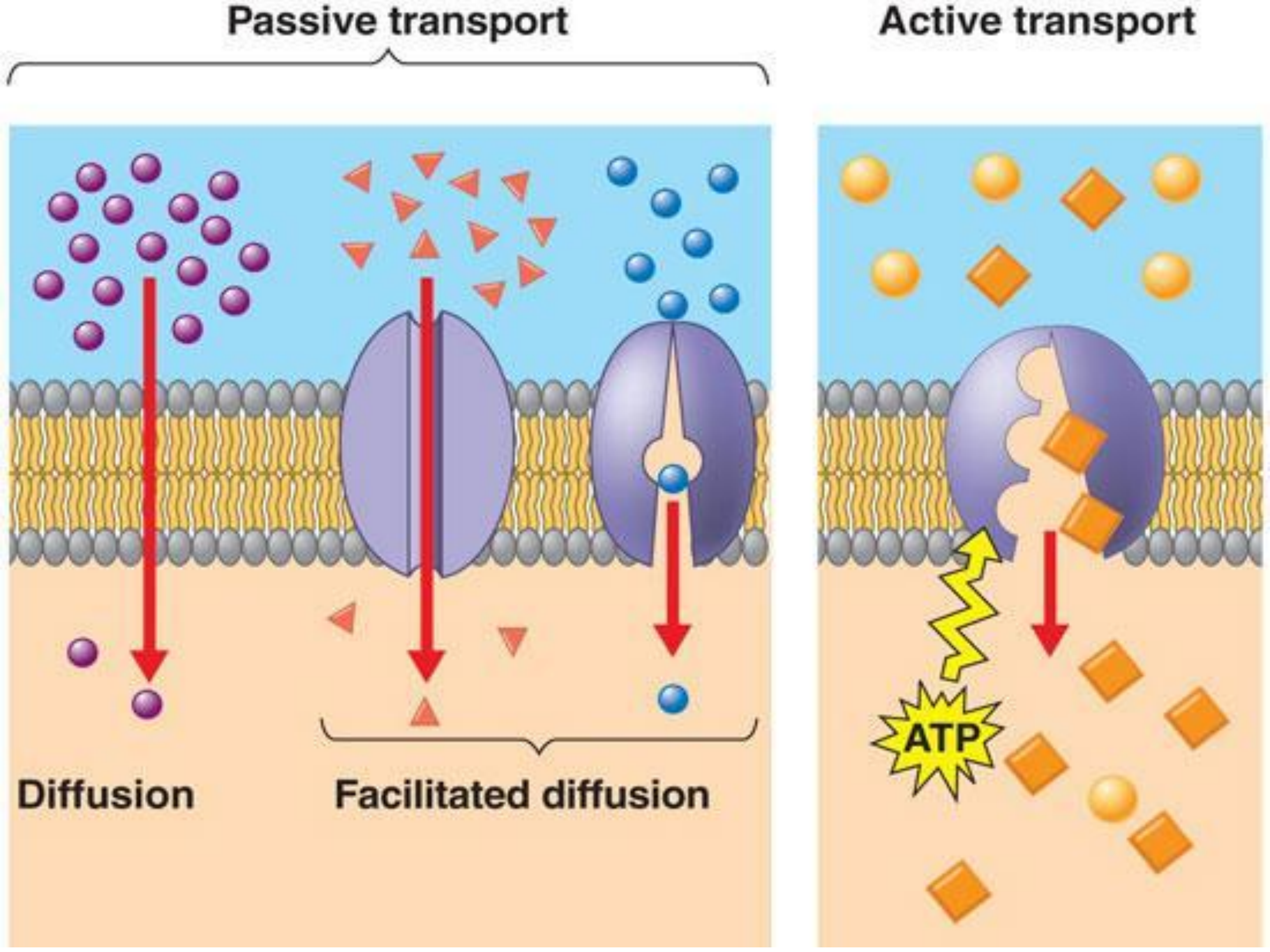
- Gated channels
- Ungated channels

- Transport according to concentration gradient (facilitated diffusion)

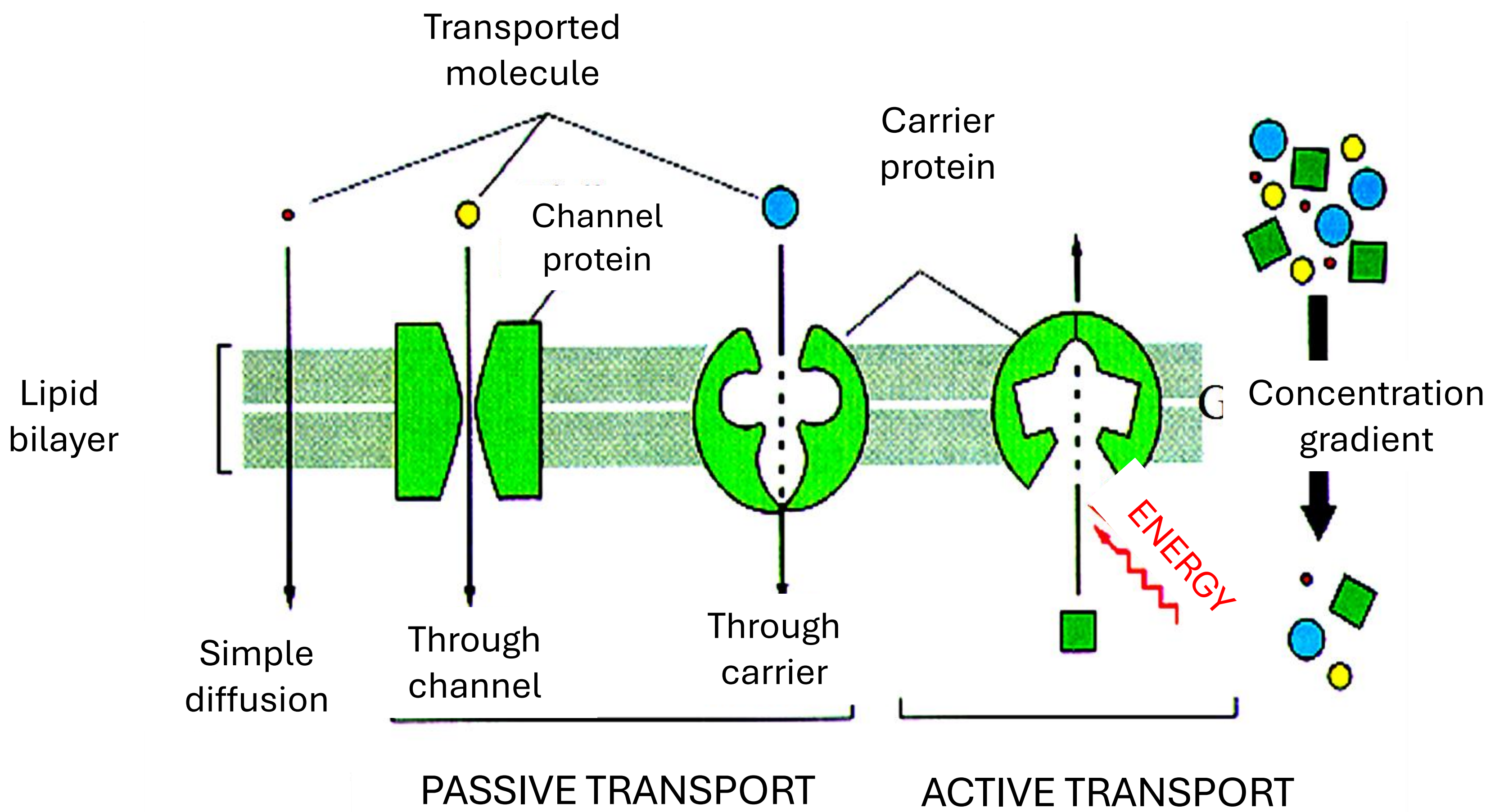
CARRIER PROTEINS

- are mainly multipass proteins that undergo reversible conformational changes

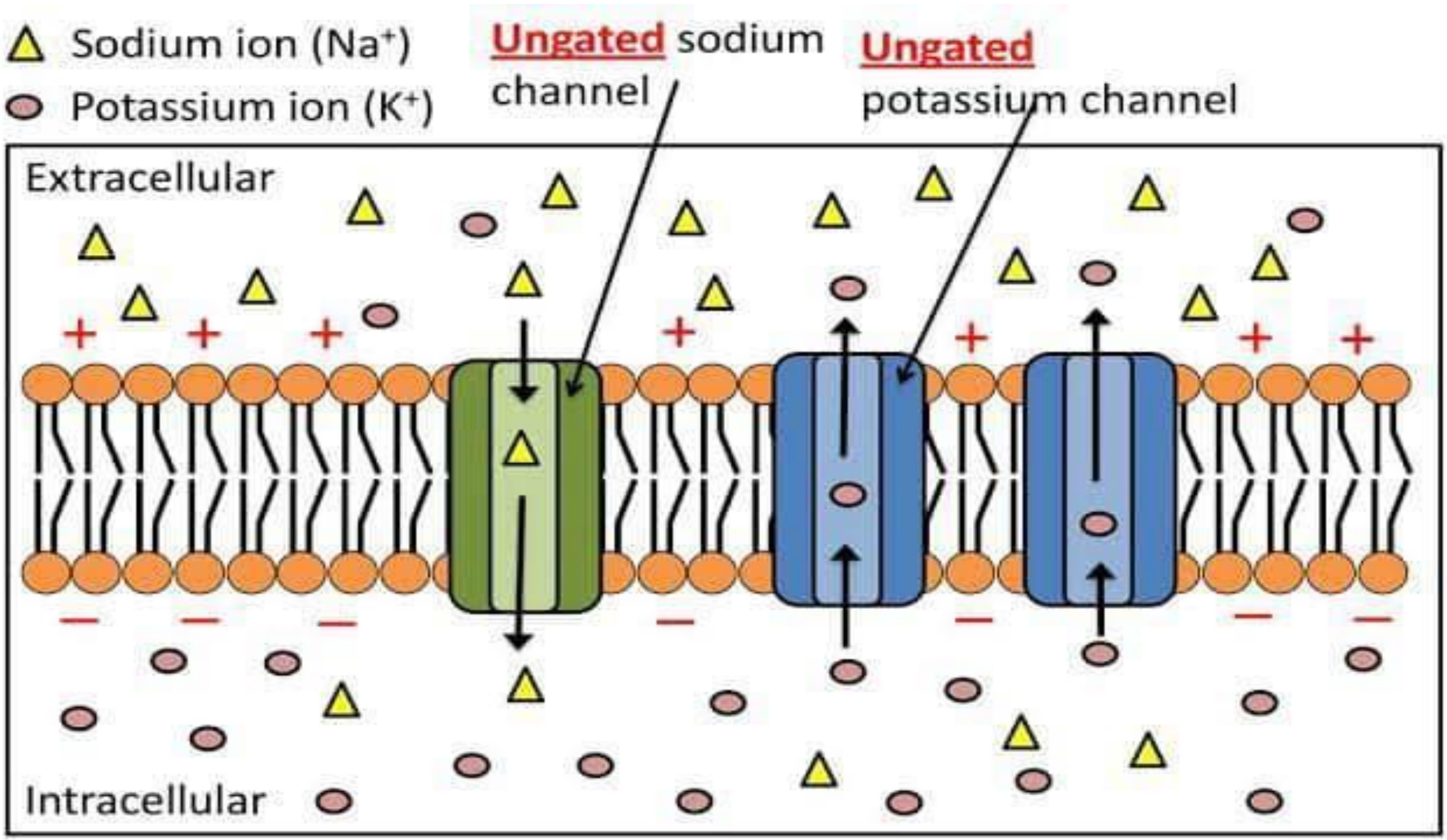
- Passive and active transport


Passive transport
Active transport
ATP
Diffusion
Facilitated diffusion

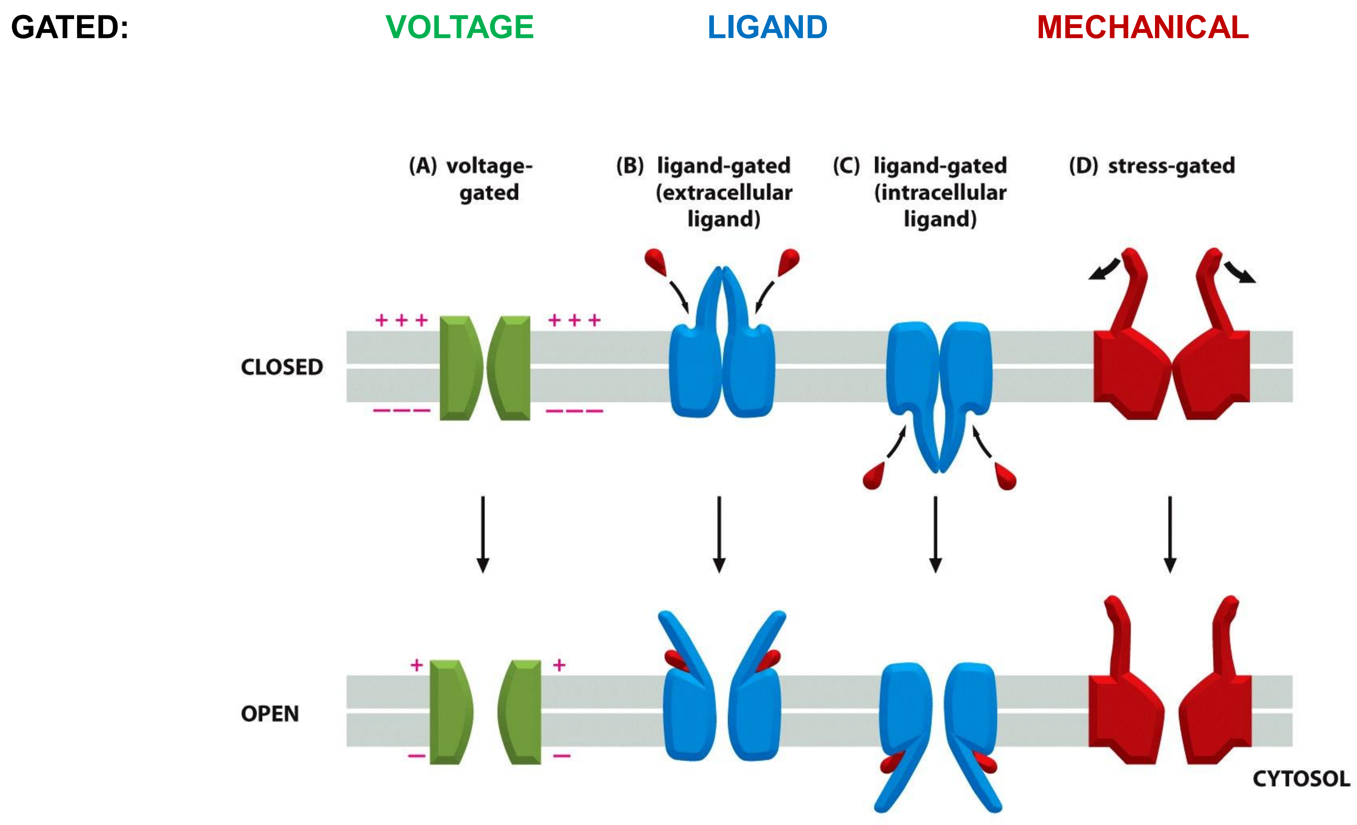
# Comparison of passive and active transport



Ungated ion channels - leak channels for Na+ and K+ ions (1:100). Resting potential



# Gated ion channels

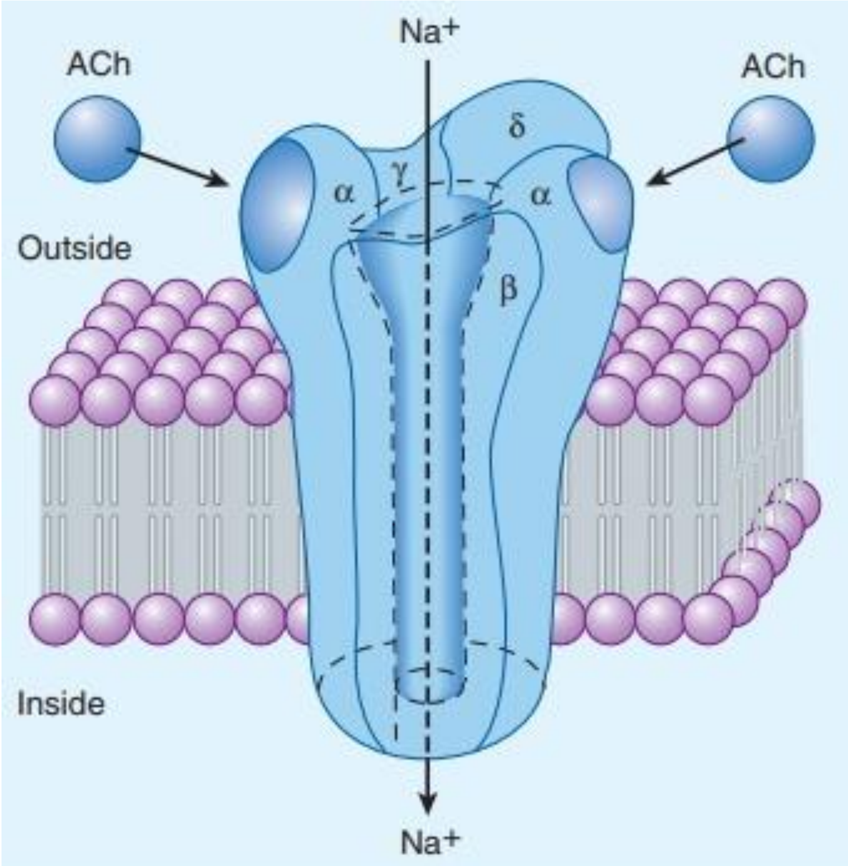



A) Sodium, calcium, potassium channels

B) Receptor for acetylcholine, GABA, glutamate, serotonin

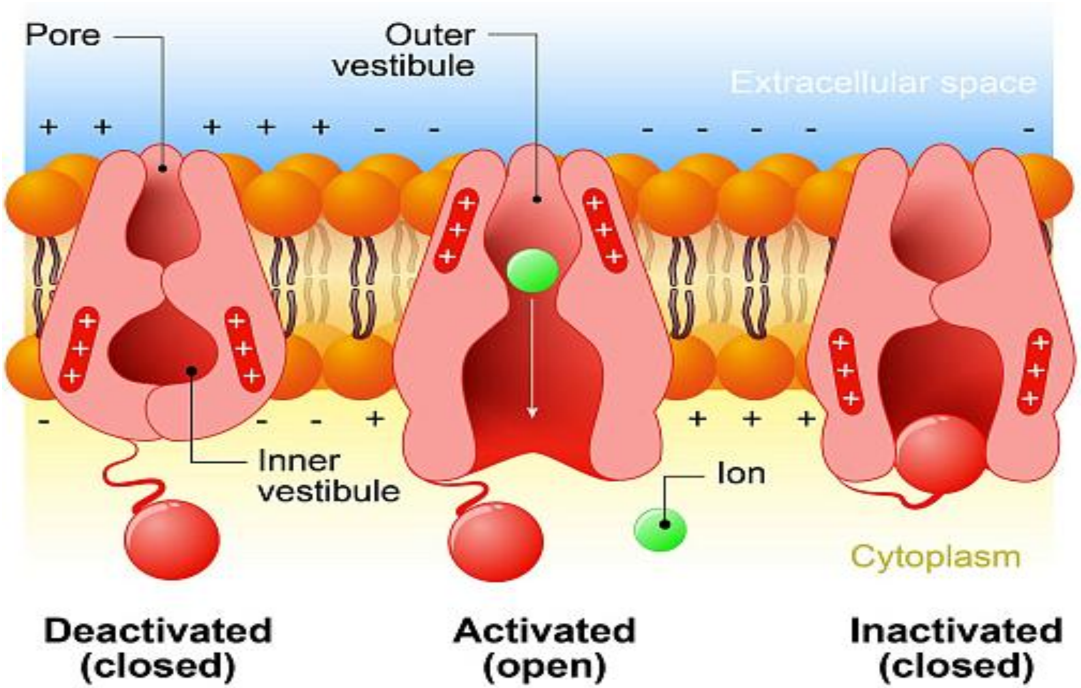
C) Pain and vibration receptors, hair cells vestibular apparatus and the organ of Corti

# Ligand-gated ion channels




Nicotinic receptor for acetylcholine – ligand-gated ion channel. After the attachment of the neurotransmitter (Ach), the channel present in the postsynaptic membrane opens and Na+ ions flow into the cytosol of the cell, changing the resting potential of the cell into an action potential (depolarization wave)

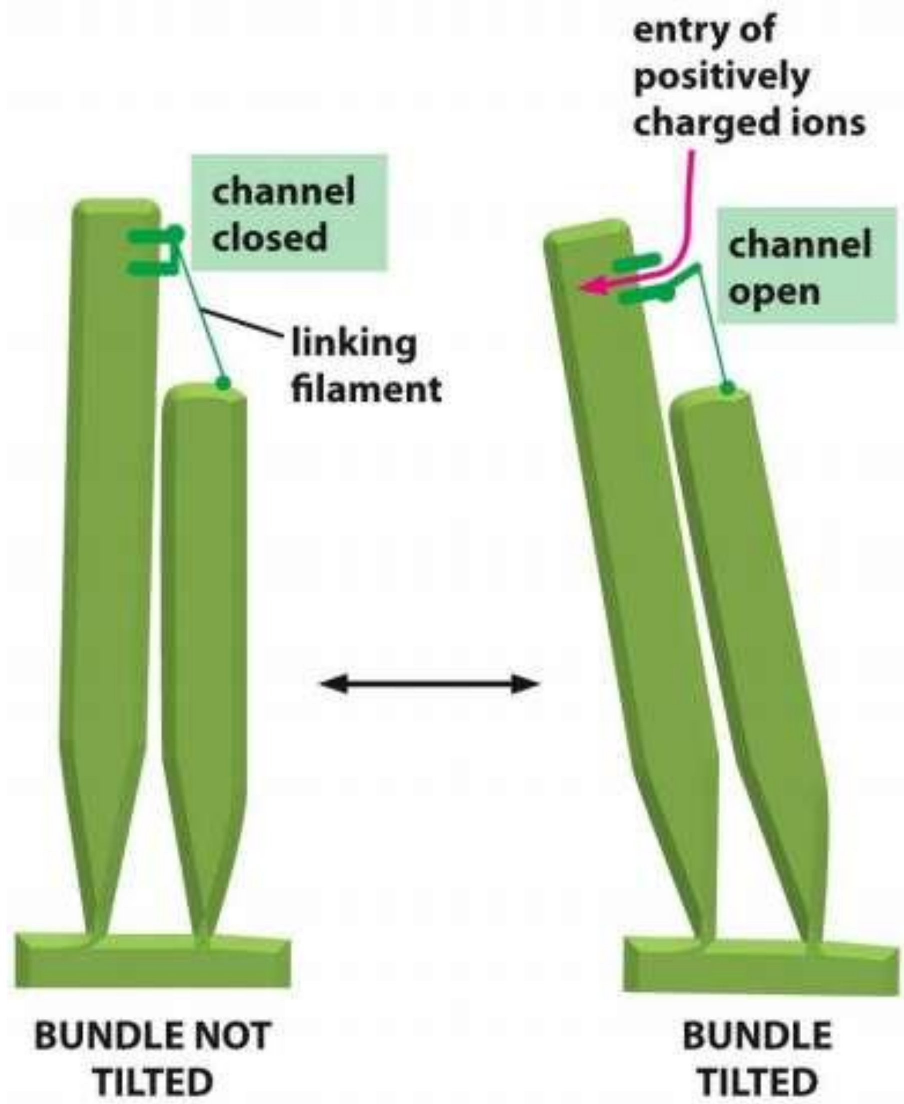
## Voltage-gated ion channels



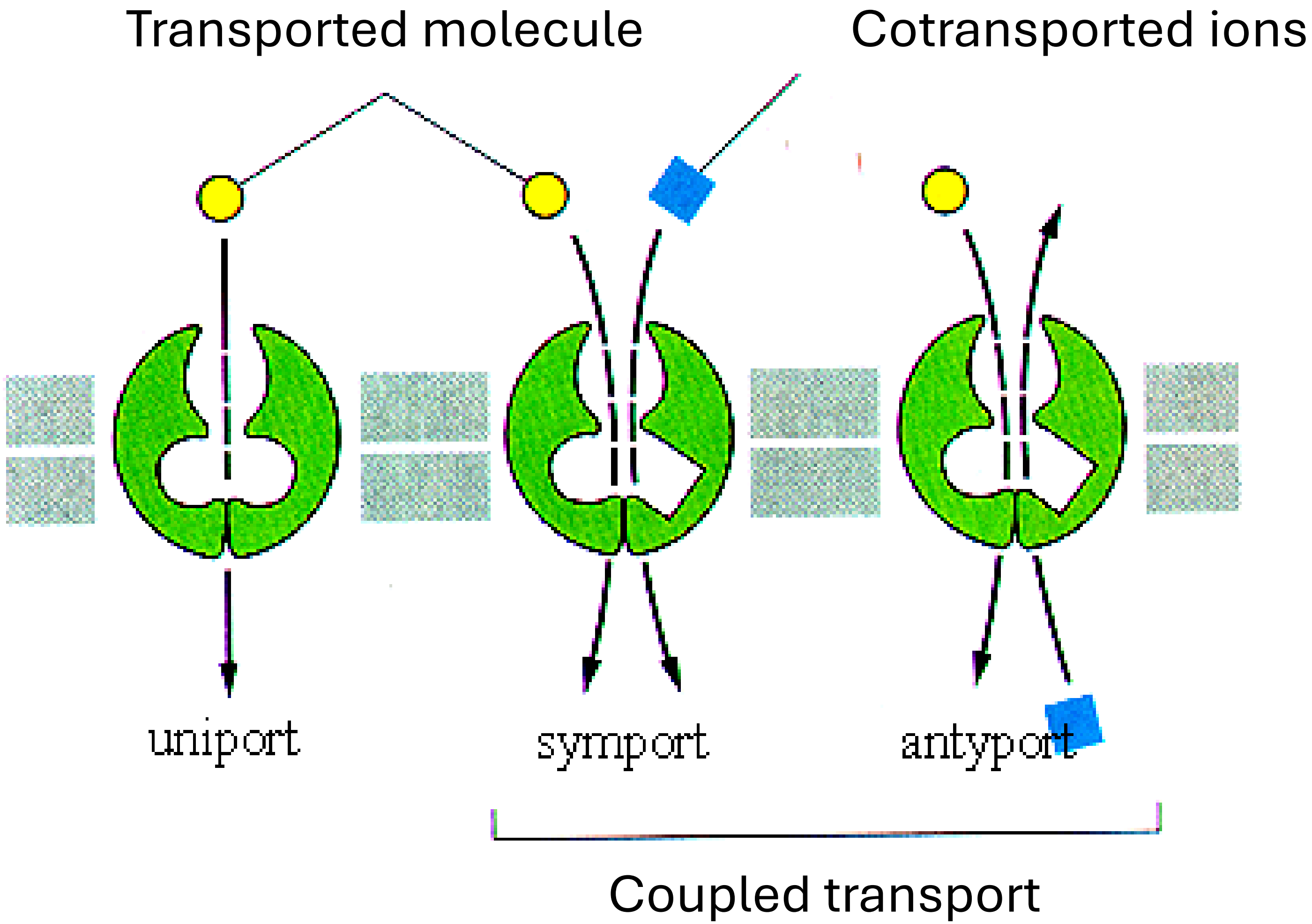

opened by the depolarization wave, Na+ ions flow into the cytosol and the depolarization wave propagates along the cell membrane.
After the depolarization wave passes, the channel is temporarily inactivated – the refraction period, the depolarization wave cannot change direction.
Only after a refractive period (milliseconds) is the channel closed, but it can already be activated.

**Corti's hair cells (stress-gated)**

Under the influence of a mechanical impulse, the stereocilia bend and potassium channels open, followed by calcium channels and exocytosis of neurotransmitters



# Three ways to transport with carrier protein



## Transport with carrier protein

**Uniport**

Sodium channel, potassium channel, calcium pump (transport of calcium ions from cytosol to ER), proton pump in the lysosome membrane, aquaporins, glucose transporters

**Symport**

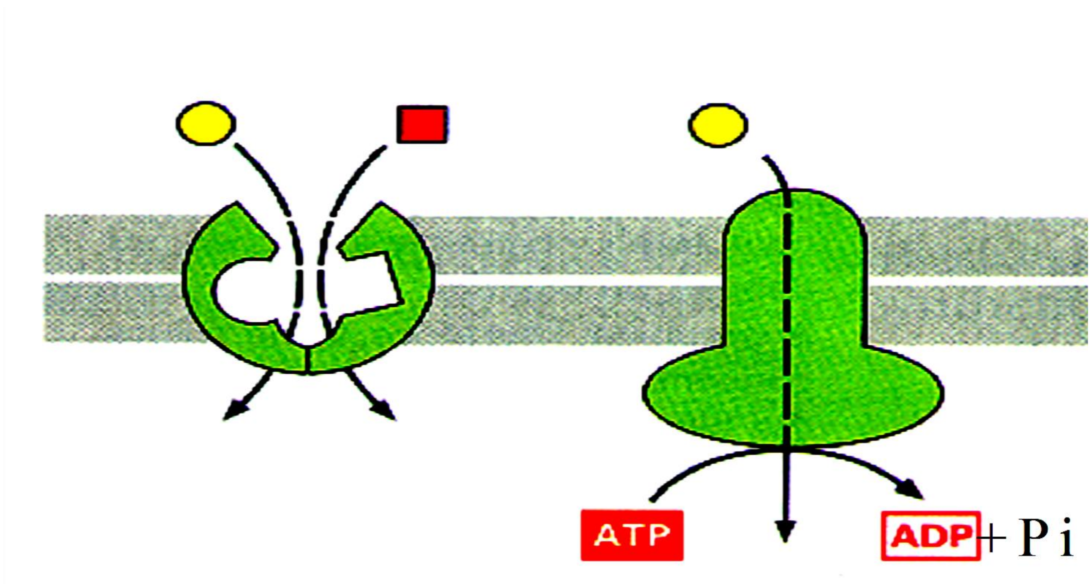
Transport of glucose with sodium ions to enterocytes

$Na^+$: glucose -2:1

**Antyport**

Ion exchangers: $Na^+/H^+$ (Henle loop); $Na^+/Ca^+$ (heart), sodium-potassium pump (resting potential)

# Forms of active transport




Secondary transport

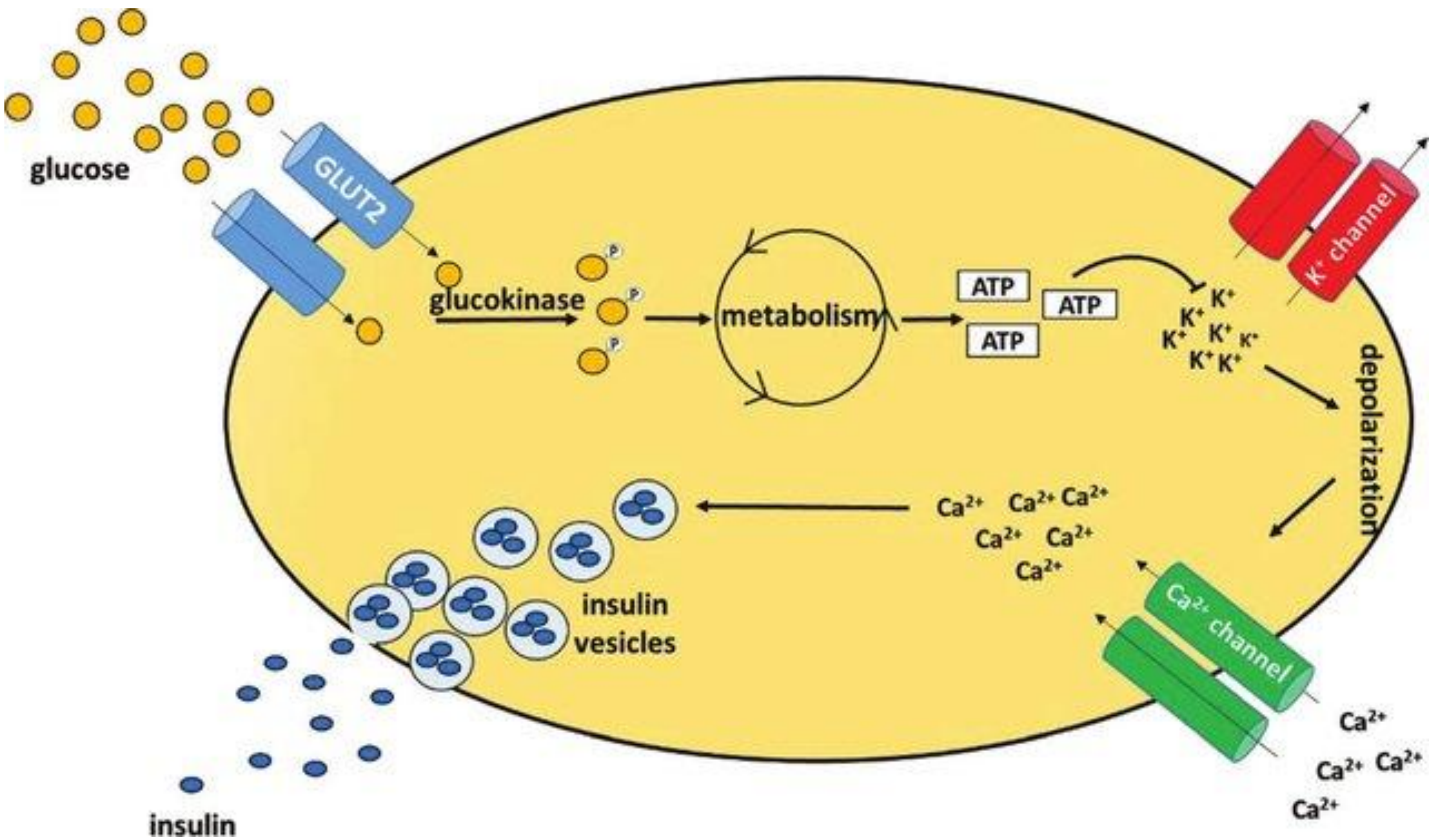
energy from the production of an electrochemical gradient.

Primary transport

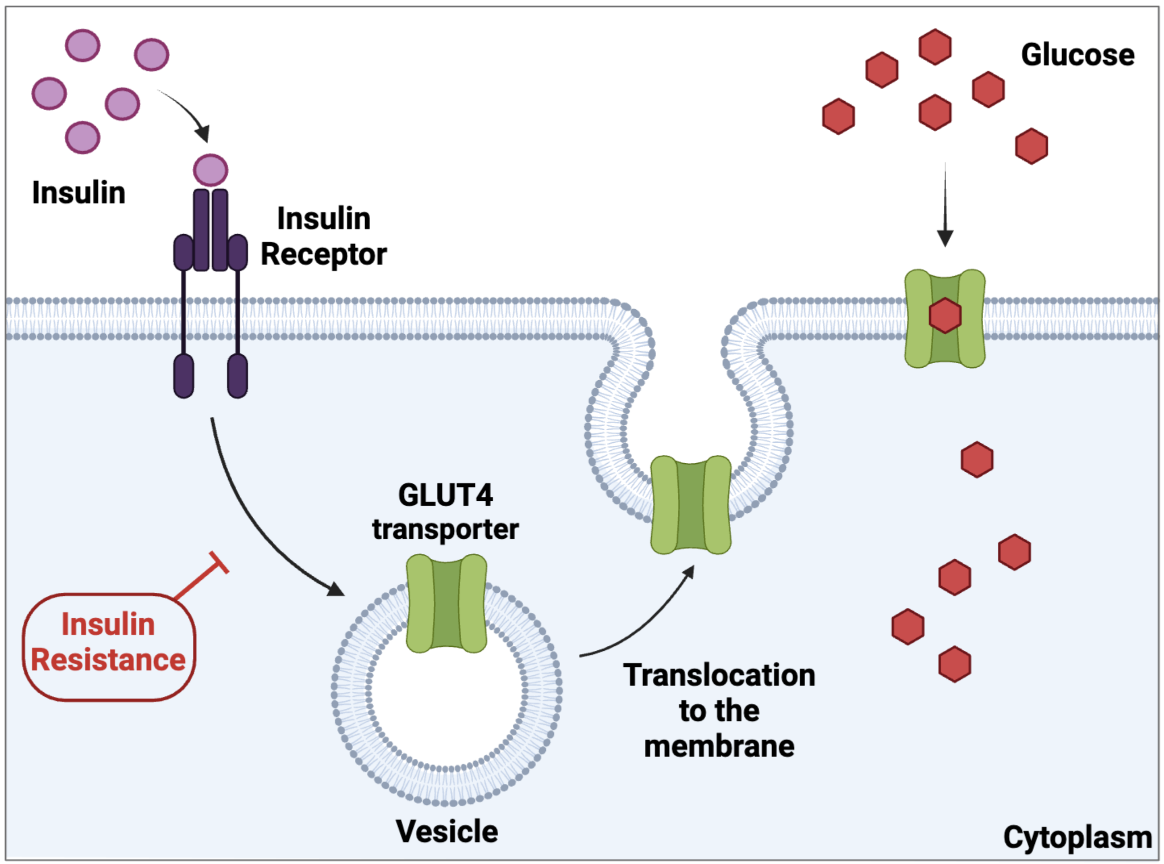
energy from ATP hydrolysis

| | |
|---|---|
| GLUT1 | - in fetal tissues. in adults - in erythrocytes and endothelial cells<br>- high affinity<br>-<br>- insulin independent |
| GLUT2 | - bidirectional tyansporter<br>- renal tubules, liver, pancreatic beta cells and small intestine epithelium - glucose uptake and release by liver cells - glycolysis, gluconeogenesis<br>- Insulin-independent low-affinity isoform |
| GLUT3 | - Neurons (the main glucose transporter in the brain), placenta, sperm<br>- Insulin-independent high-affinity isoform |
| GLUT4 | - adipose tissue and striated muscles (skeletal muscles and heart muscle)<br>- insulin-regulated glucose transporter. |
| GLUT5 | - fructose transporter in enterocytes in the small intestine, as well as in skeletal muscle, nuclei, kidneys, adipocytes and brain |

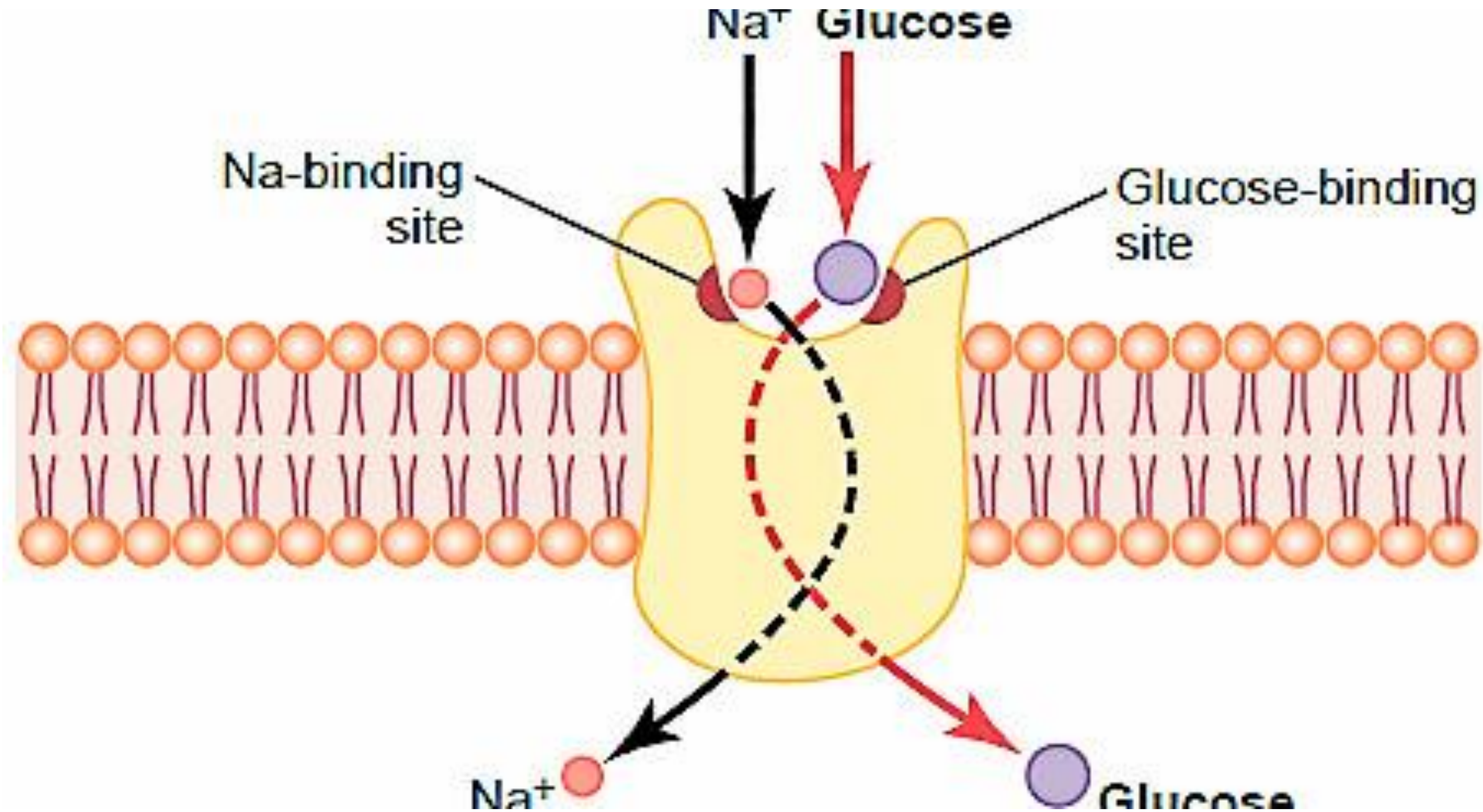
# GLUT 2 and pancreatic islet beta cells



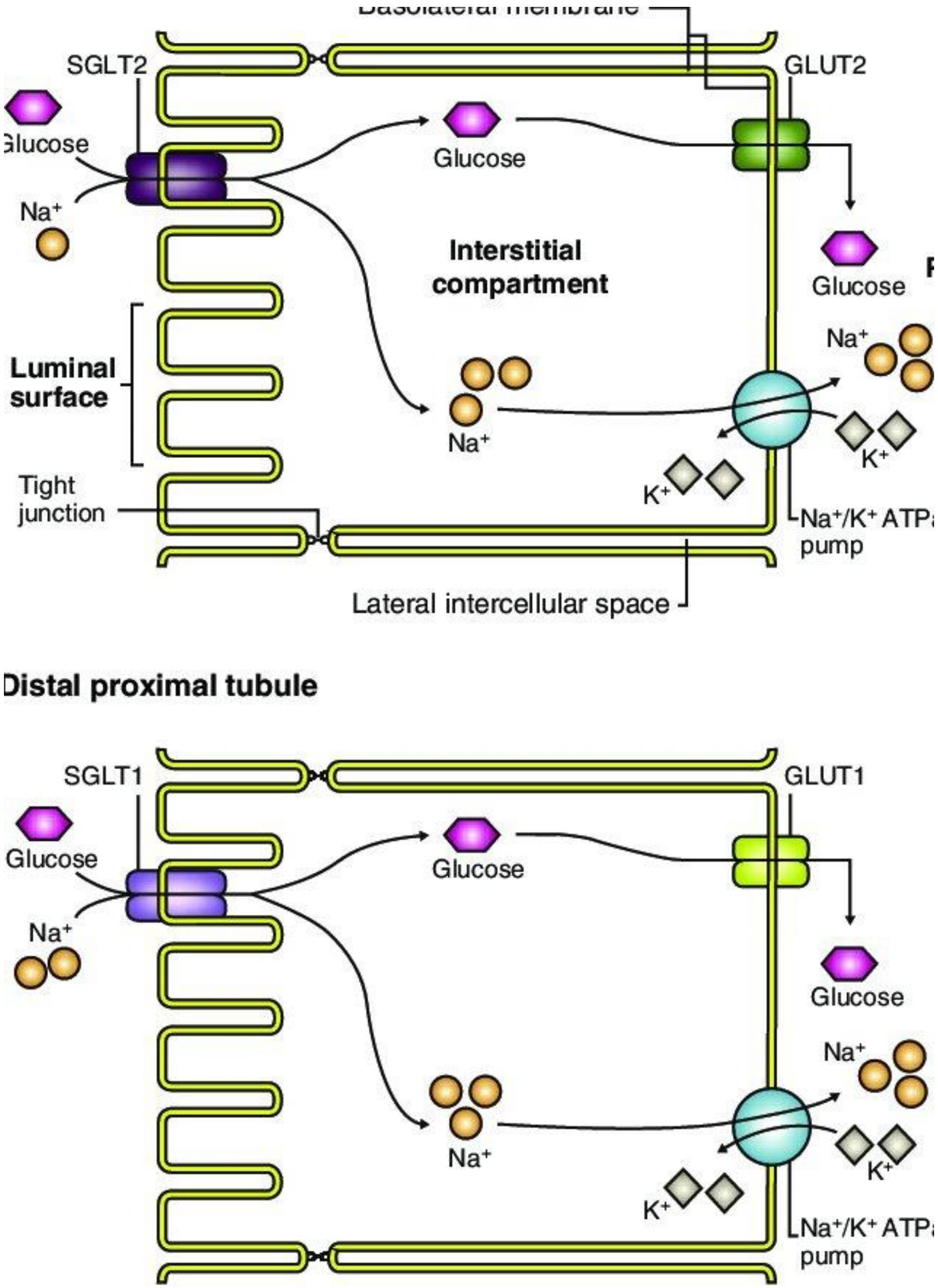
# GLUT 4 is insulin sensitive



# SGLT

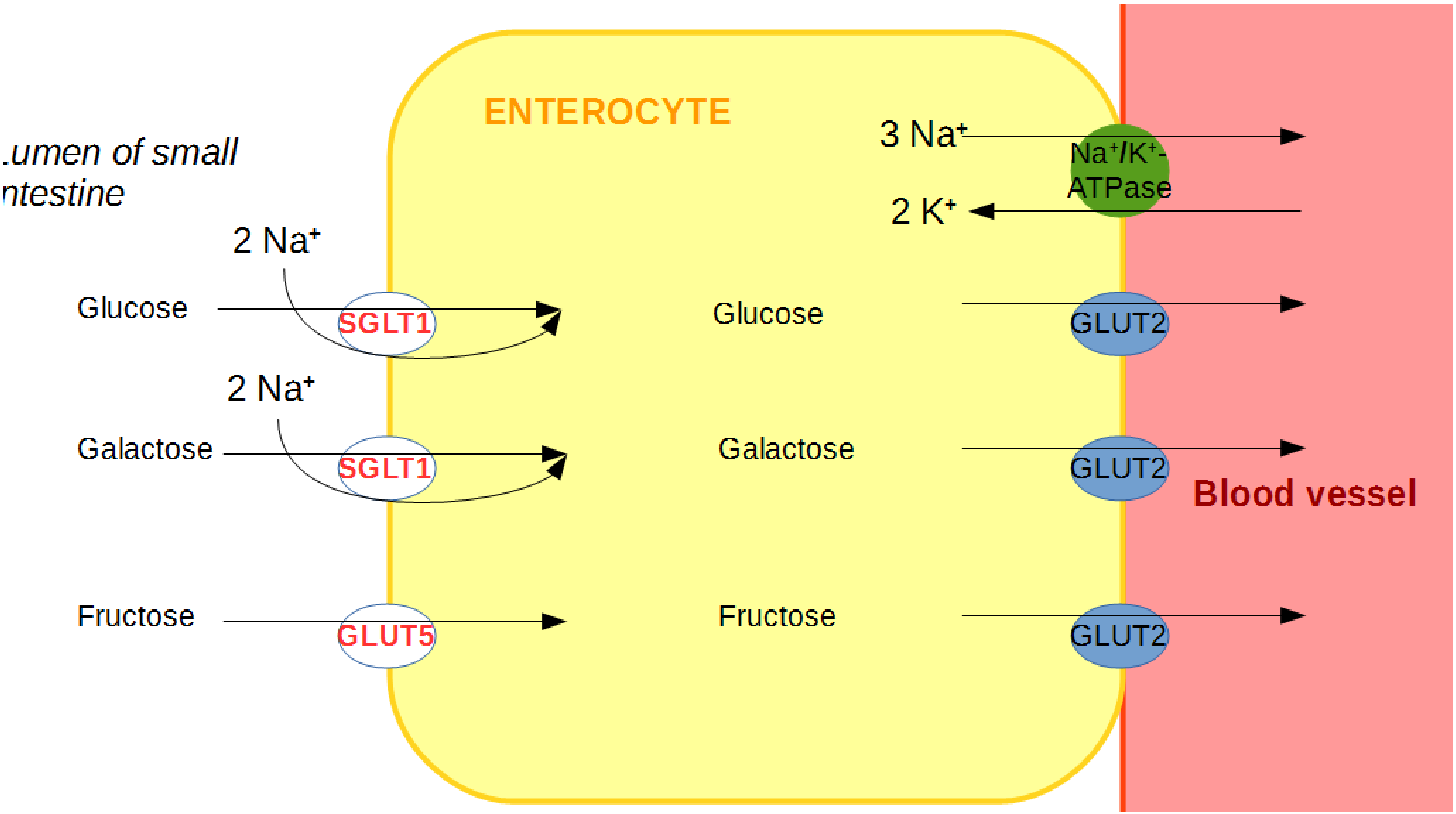



Sodium-dependent glucose cotransporters (or sodium-glucose-coupled transporters, SGLT) are found in enterocytes (SGLT1) and the proximal tubule of the nephron (SGLT2 in PCT and SGLT1 in PST). They participate in the reabsorption of glucose. In the kidneys, 100% of the filtered glucose must be reabsorbed by the nephron (98% in PCT, by SGLT2).

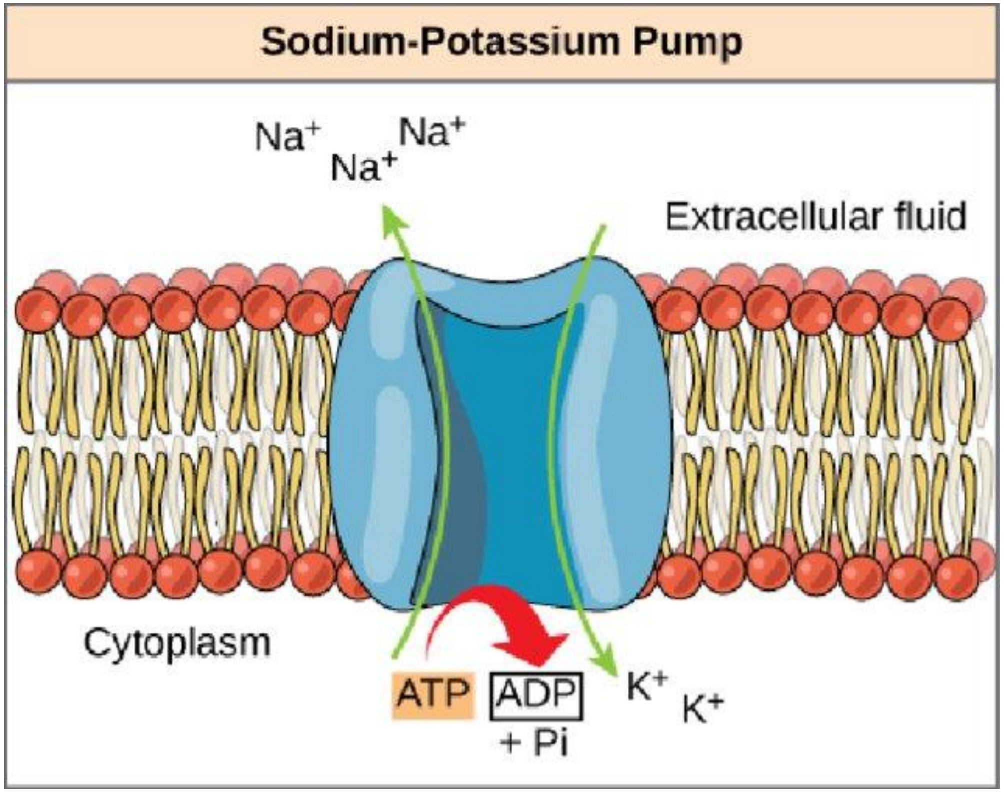



2 types of transporters work together in the cells of the proximal tubules of the kidney, with the sodium-glucose cotransporter transporting glucose into the cell through the apical membrane and the glucose uniporter transporting glucose through the basal-lateral membrane into the blood.

# Coupled sodium-glucose transporter, SGLT1 - a glucose transporter found in the intestinal mucosa (enterocytes) of the small intestine



# SODIUM-POTASSIUM PUMP – ANTIPORT




**A single ATP-ase at the expense of hydrolysis of one ATP molecule transports up to 300 Na+ ions and 200 K+ ions per second.**

Generation of resting potential, including leak channels for sodium and potassium ions

# Calcium Pump

Uniportal active transport of calcium ions from the cytosol to the endoplasmic reticulum lumen

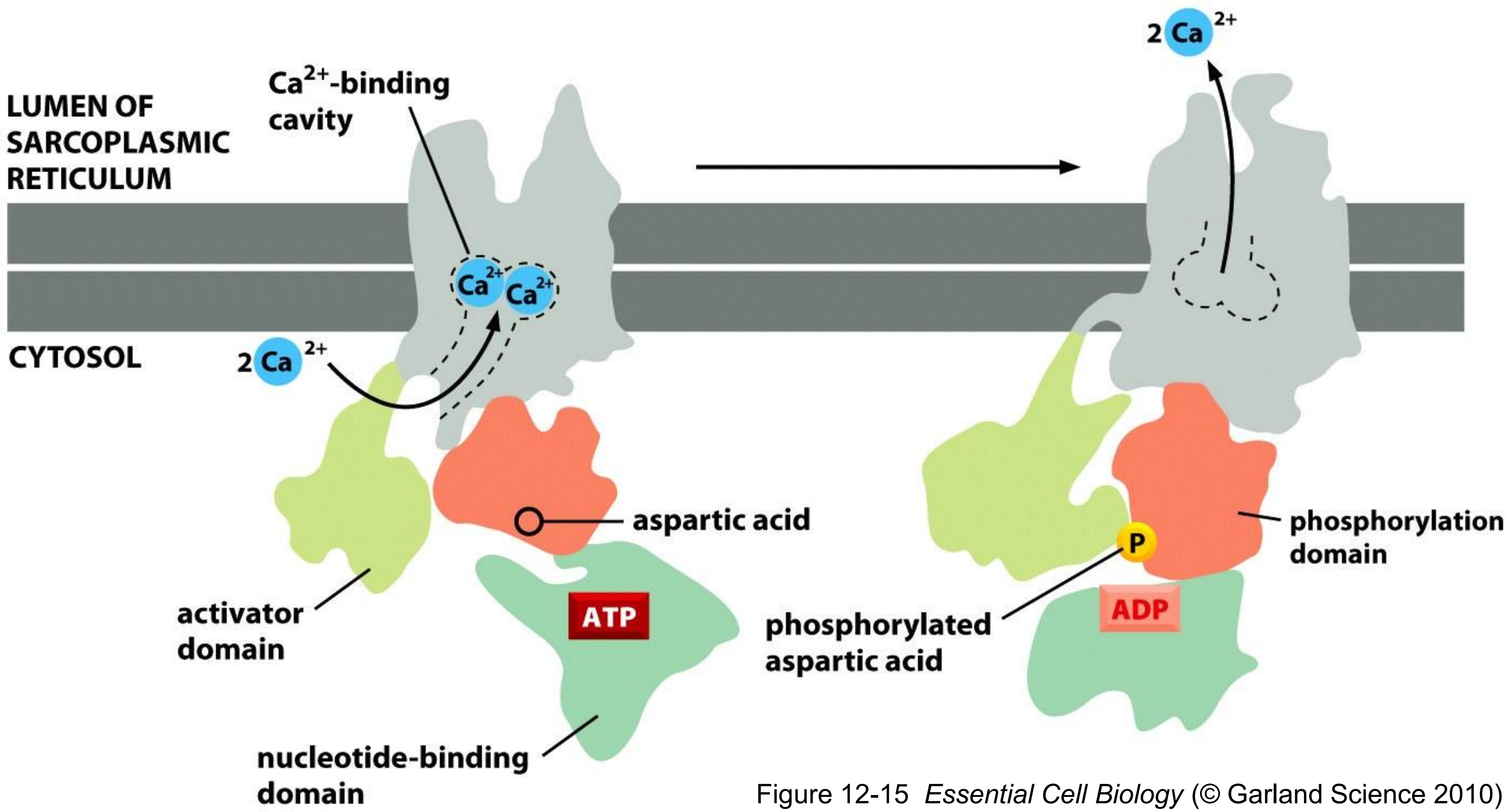
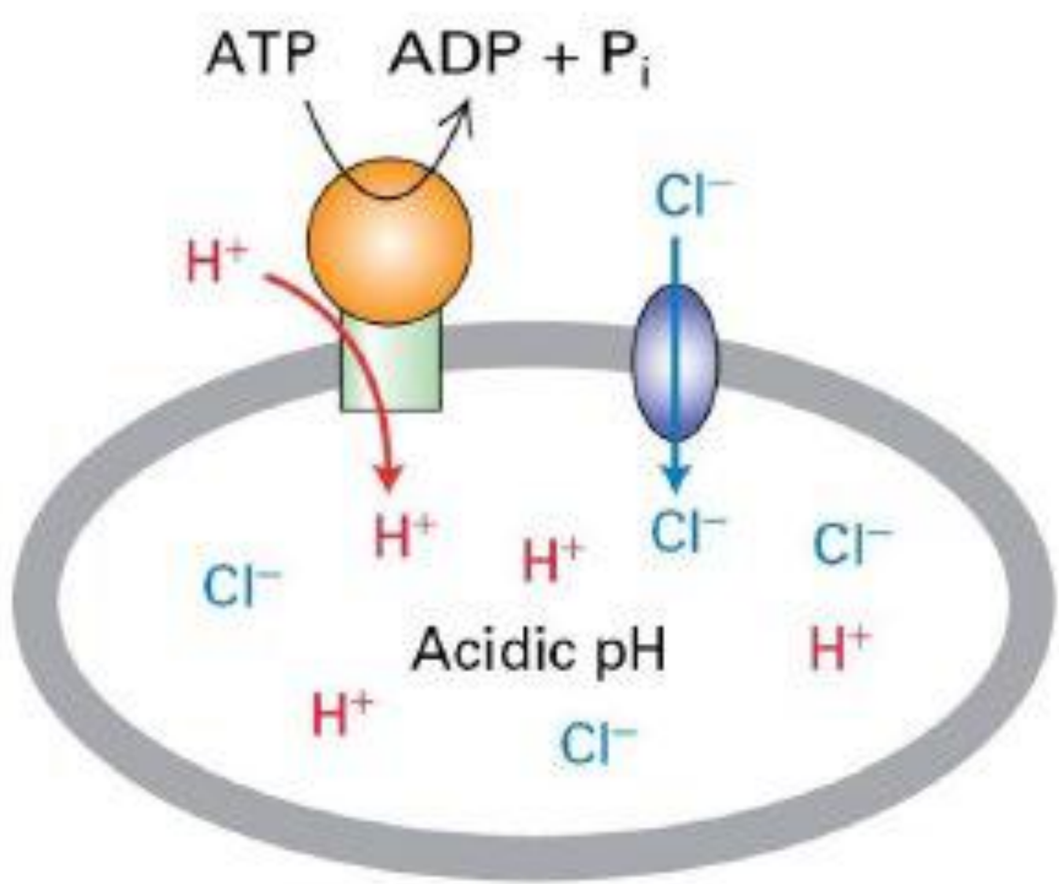



Figure 12-15 *Essential Cell Biology* (© Garland Science 2010)

* In cardiomyocyte sarcolemma, the antiport 3 Na+↓ / Ca2+↑

Proton pump v-ATPase present in lysosome and endosome membranes



# Cystic fibrosis.

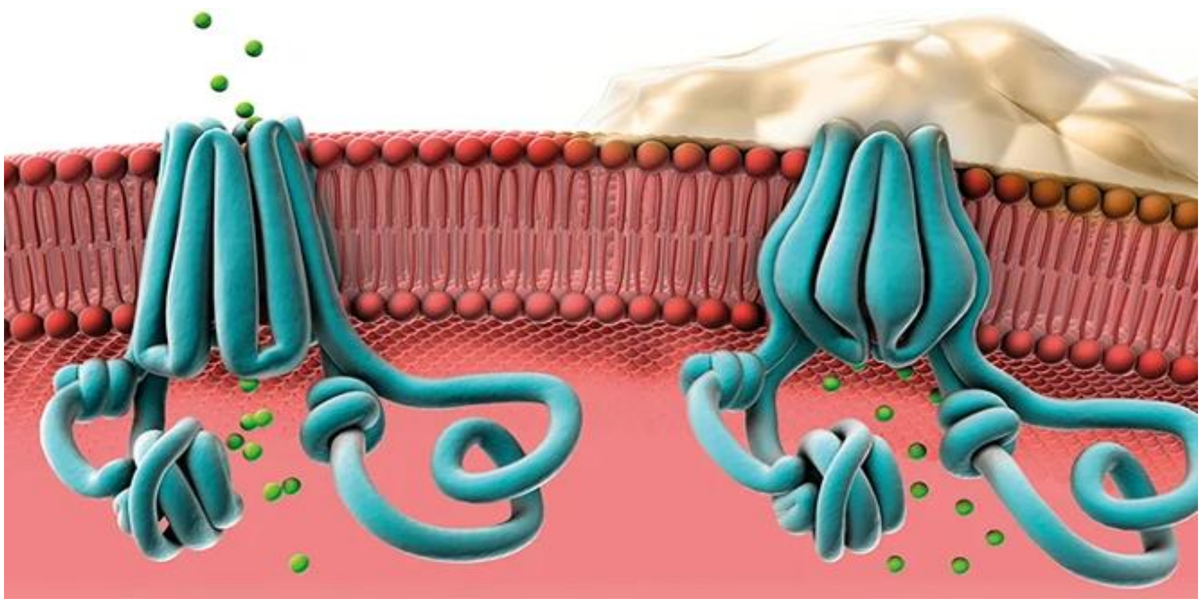
A genetically determined disease consisting in a disorder of secretion by the exocrine glands.

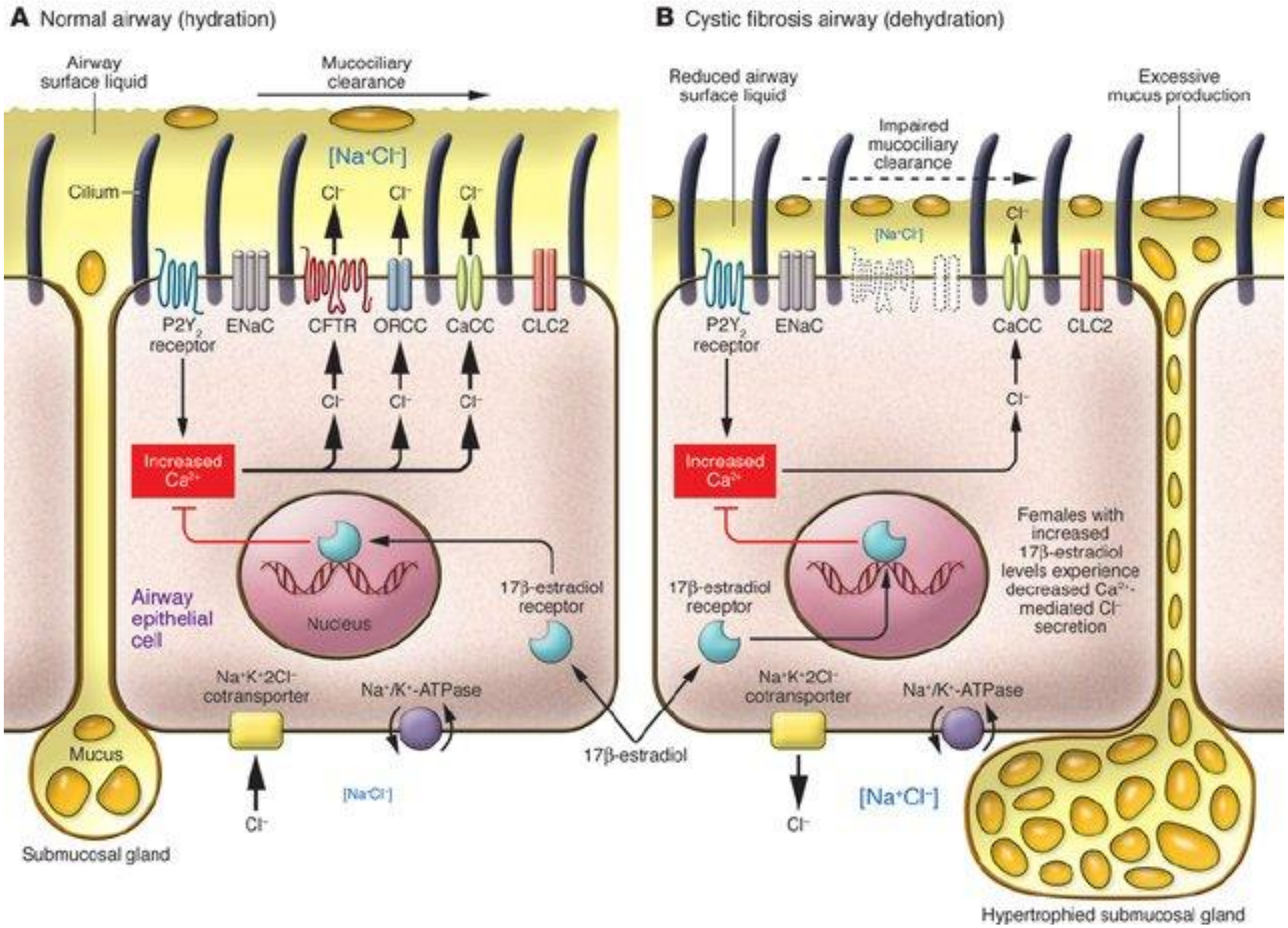
Symptoms:

respiratory system – recurrent infections that lead to lung damage and respiratory failure

digestive tract – chronic inflammation of the pancreas, leads to insufficiency

Mutations in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel

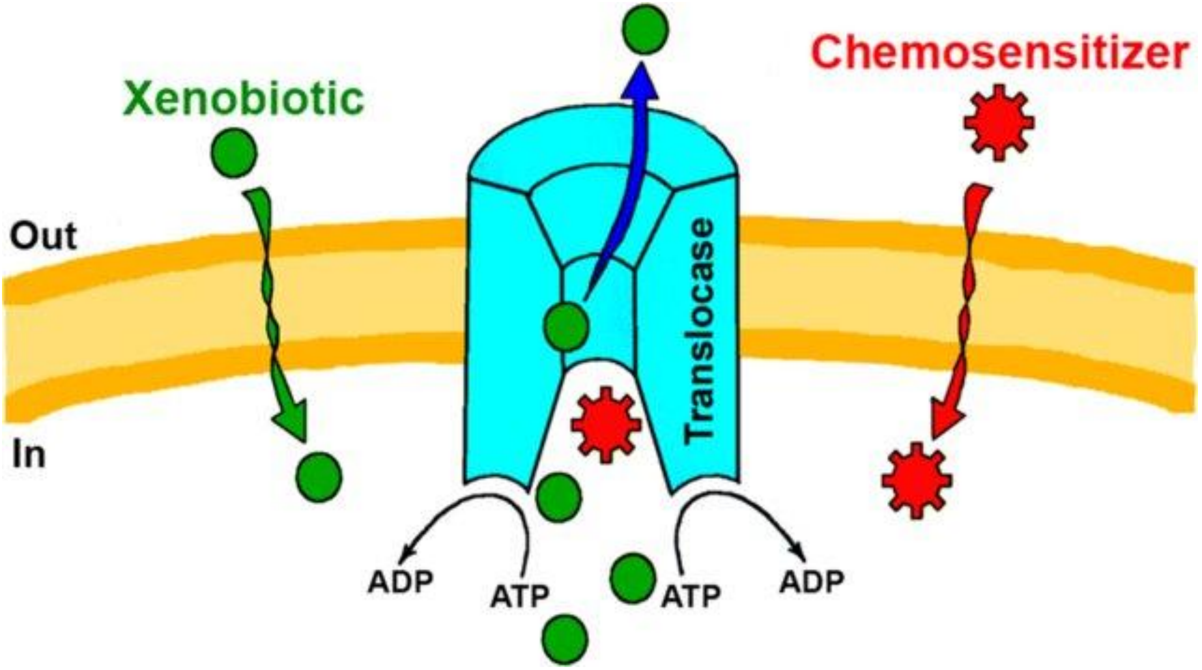





ENaC - epithelial sodium channel, whose activity under normal conditions is inhibited by an active CFTR.

# Glycoprotein-P

ATP-binding cassette sub-family B member 1 (ABCB1) multidrug resistance protein 1 (MDR1) - **multidrug resistance protein**, transporter ABC - translocase, with a different tissue distribution in humans. Overexpression of P-gp (gene amplification) leads to a decrease in the intracellular concentration of many chemotherapeutics. ABC transporter inhibitors can be used in combination with chemotherapy drugs to increase their effectiveness



ATP-binding cassette super-family G member 2 is a protein, **ABC transporter**, breast cancer resistance protein **(BCRP)**.

This protein acts as a transporter of xenobiotics, which causes multidrug resistance of cells to chemotherapeutic drugs

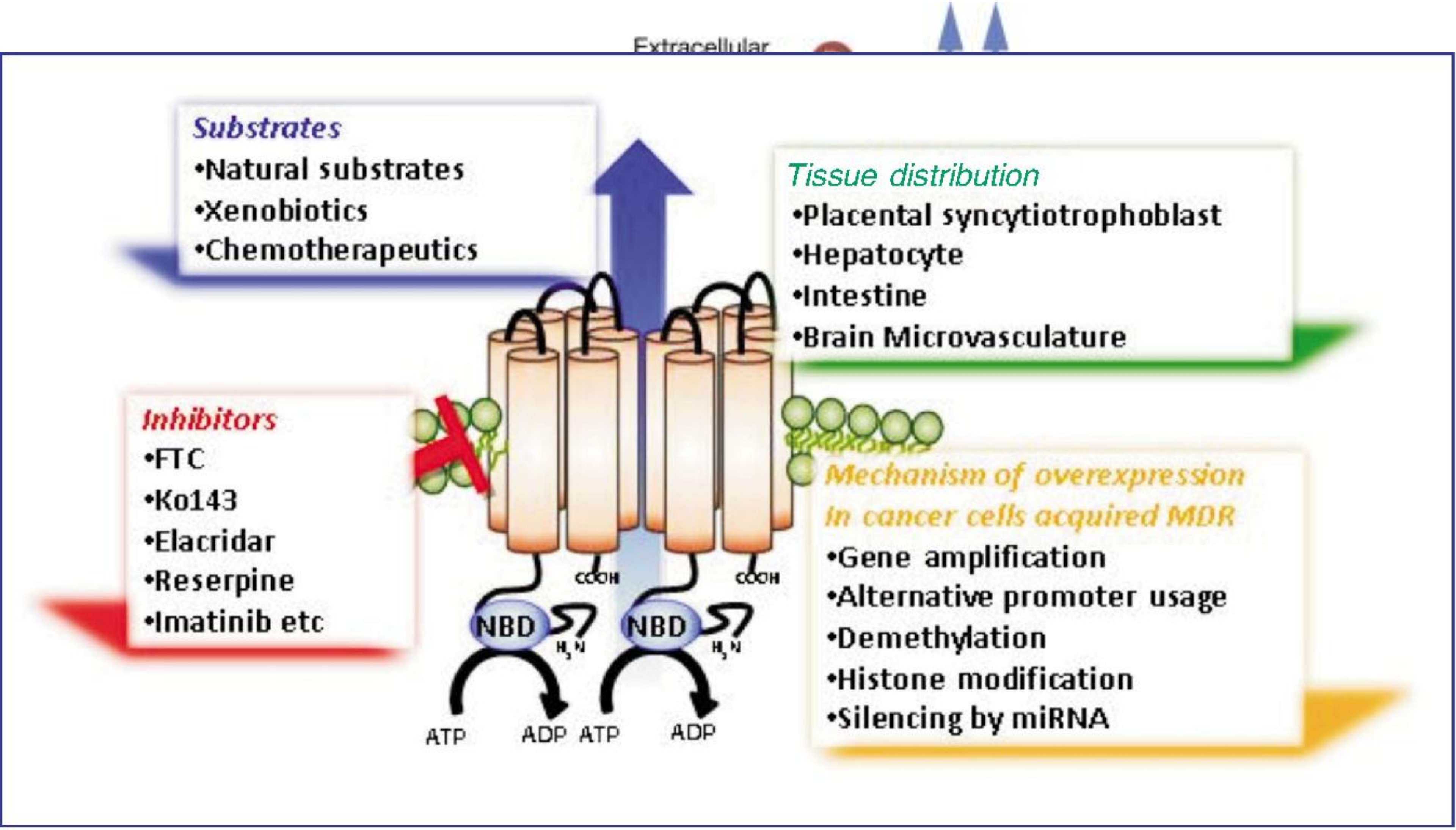
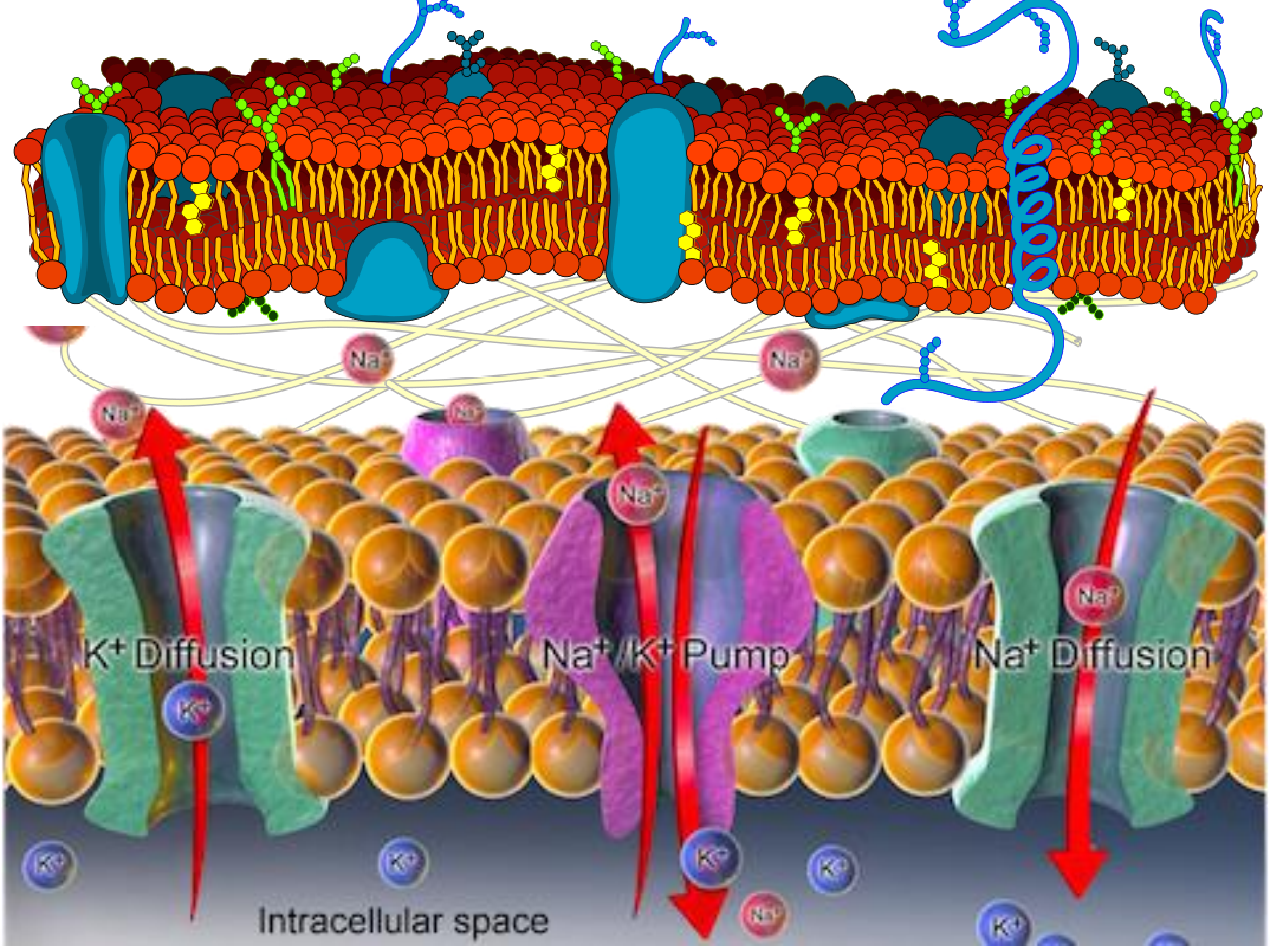



Figure 1. **Summary of BCRP function, tissue distribution, and mechanism of overexpression in drug-resistant cancer cells.** BCRP consists of 6 transmembrane helices and homodimerizes to function at the plasma membranes. It pumps natural substrates, including folate, steroid hormones,


K+ Diffusion
Na+/K+ Pump
Na+ Diffusion
Intracellular space